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Medical History, Lifestyle, Family History, and Occupational Risk Factors for Mycosis Fungoides and Sézary Syndrome: The InterLymph Non-Hodgkin Lymphoma Subtypes Project

Briseis Aschebrook-Kilfoy, Pierluigi Cocco, Carlo La Vecchia, Ellen T. Chang, Claire M. Vajdic, Marshall E. Kadin, John J. Spinelli, Lindsay M. Morton, Eleanor V. Kane, Joshua N. Sampson, Carol Kasten, Andrew L. Feldman, Sophia S. Wang, Yawei Zhang

Correspondence to: Yawei Zhang, PhD, Department of Environmental Health Sciences, Yale School of Public Health, 60 College Street, New Haven, CT 06520 (e-mail: yawei.zhang@yale.edu)

Background Mycosis fungoides and Sézary syndrome (MF/SS) are rare cutaneous T-cell lymphomas. Their etiology is poorly understood.

Methods A pooled analysis of 324 MF/SS cases and 17 217 controls from 14 case–control studies from Europe, North America, and Australia, as part of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma (NHL) Subtypes Project, was carried out to investigate associations with lifestyle, medical history, family history, and occupational risk factors. Multivariate logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI).

Results We found an increased risk of MF/SS associated with body mass index equal to or larger than 30 kg/m^2 (OR = 1.57, 95% CI = 1.03 to 2.40), cigarette smoking for 40 years or more (OR = 1.55, 95% CI = 1.04 to 2.31), eczema (OR = 2.38, 95% CI = 1.73 to 3.29), family history of multiple myeloma (OR = 8.49, 95% CI = 3.31 to 21.80), and occupation as crop and vegetable farmers (OR = 2.37, 95% CI = 1.14 to 4.92), painters (OR = 3.71, 95% CI = 1.94 to 7.07), woodworkers (OR = 2.20, 95% CI = 1.18 to 4.08), and general carpenters (OR = 4.07, 95% CI = 1.54 to 10.75). We also found a reduced risk of MF/SS associated with moderate leisure time physical activity (OR = 0.46, 95% CI = 0.22 to 0.97).

Conclusions Our study provided the first detailed analysis of risk factors for MF/SS and further investigation is needed to confirm these findings in prospective data and in other populations.

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Mycosis fungoides and Sézary syndrome (MF/SS) are mature T-cell lymphomas that originate in the skin. The age-adjusted incidence rate per 100 000 person-years in the United States in 2005–2008 was 0.01 for SS and 0.55 for MF (1), with the latter showing a slight increase compared with the rate of 0.41 per 100 000 person-years in 2001–05 (1,2). While the age-adjusted incidence rates vary between countries, a slightly increased incidence of MF has also been reported in Norway (3) and Japan (4) over the past decades. The incidence of MF/SS is around 1.5 times higher in males than females (2,3). In the United States, the highest incidence rate of MF is observed among African Americans, with a black-to-white incidence rate ratio of 1.55 (2).

MF presents in the skin with patches/plaques and is characterized by epidermal and dermal infiltration of small to medium-sized T cells with cerebriform nuclei (5). MF generally has a long natural history and is likely to be diagnosed at an early stage, resulting in a generally good prognosis with a median survival of more than 25 years (6,7). SS is characterized by the presence of erythroderma, lymphadenopathy, and neoplastic T lymphocytes in the blood and its behavior is much more aggressive with a median survival of about 5 years (6,7).

Because of the rarity of these diseases, very few epidemiologic studies on MF/SS risk factors have been conducted thus far, and the only identified risk factors are male gender, advanced age, and African American descent (8). Smoking and alcohol consumption (9), several occupations and the related exposures (9–12), atopic diseases (9,13), sun exposure (14,15), and several infectious agents such as human herpesvirus 8, hepatitis C virus (HCV), *Borrelia burgdorferi*, and cytomegalovirus (16–20) have been studied, but their roles in the etiology of MF/SS remain unestablished.

To advance our understanding of MF/SS etiology, we investigated associations with lifestyle, medical history, family history, and occupational risk factors in a pooled analysis of 324 cases and 17 217 controls from 14 case-control studies from Europe, North America, and Australia as part of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma (NHL) Subtypes Project.

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 MF/SS, and 2) availability of individual-level data for at least several risk factors of interest by December 31, 2011. 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 written, informed consent before interview.

NHL Subtype Ascertainment and Harmonization

Cases were classified according to the World Health Organization classification (5,21) 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 to confirm the diagnoses. Each participating study's pathology review procedures, rules for NHL subtype classification, and NHL subtype distribution were reviewed by an interdisciplinary team of pathologists and epidemiologists.

Risk Factor Ascertainment and Harmonization

Each study collected data on putative NHL risk factors in a standardized, structured format by in-person or telephone interviews and/or self-reported questionnaires. Risk factors selected for inclusion in this analysis were lifestyle, medical history, family history, and occupational risk factors with data from at least four studies. Centralized harmonization of de-identified individual-level data from each study was a key element of the project. Each exposure variable was harmonized separately, before being reviewed for consistency among related exposure variables. Details of the data harmonization rules are provided elsewhere in this issue.

Statistical Analysis

Risk of MF/SS associated with each exposure variable was examined using logistic regression models adjusted for age, race/ethnicity, and gender. Statistical significance of each relationship 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. To evaluate effect heterogeneity among the 14 studies, we performed a separate logistic regression within each study and then quantified the variability of the coefficients by the H statistic, adapting the definition by Higgins and Thompson to categorical variables (24).

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 possible effect modification, we stratified the above logistic regression analyses by age, gender, race/ethnicity, region (ie, Northern Europe, Southern Europe, North America, and Australia) study, study design (ie population-based vs. hospital-based), or other putative risk factors identified in the analysis. Also, we set multivariate regression models adjusting each risk estimate for the other putative risk factor included one at the time, and a forward step-wise single regression model including all putative risk factors. Because the results did not change substantially with use of the multivariate models, ORs are presented from the minimally adjusted models only.

Because controls for most original studies were frequency-matched to the age and gender distribution of all NHL cases, rather than just MF/SS, we conducted sensitivity analyses using a subset of controls that were frequency-matched by age and gender to cases of MF/SS. The results from these sensitivity analyses were very similar to the results obtained using the full set of controls; thus, we retained the full set of controls for our main analyses to increase statistical power.

Results

This pooled analysis included the largest number of subjects from North America (61% cases and 43% controls), followed by Northern Europe (20% cases and 34% controls), Southern Europe (17% cases and 19% controls), and Australia (1% cases and 4% controls). Most of the study population came from population-based studies (86% cases and 80% controls), with the remainder coming from hospital-based studies (14% cases and 20% controls). Of the 324 cases, 271 (84%) were MF, 13 (4%) were SS, and 40 (12%) were unclassified MF/SS; the majority (78%) of MF/SS cases were histologically classified based on the WHO Classification. Cases and controls showed similar distributions of age, gender, and socioeconomic status (Table 1). MF/SS cases had higher percentages of African Americans and Asians compared with controls (due to the distribution in US studies).

The associations between lifestyle factors and risk of MF/SS based on basic adjusted models are presented in Table 2. An increased risk was observed for people who had smoked for 40 years or longer (OR = 1.60, 95% CI = 1.08 to 2.38), and for obesity [body mass index (BMI) ≥ 30 kg/m^2: OR = 1.58, 95% CI = 1.04 to 2.41] with reference to BMI between 18.5 and 22.4 kg/m^2. However, no evidence of an increasing trend was observed with increasing years of smoking or BMI. On the other hand, compared with people who were not engaged in leisure-time physical activity, those who reported moderate (OR = 0.44, 95% CI = 0.21 to 0.91) or vigorous (OR = 0.50, 95% CI = 0.28 to 0.90) physical activity was inversely associated with a reduced risk of MF/SS. Again, no trend was detected with level of physical activity. We did not observe an association with alcohol consumption, hair dye use or sun exposure.

Among previous medical conditions, eczema was significantly associated with an increased risk of MF/SS (Table 3). Although the association was stronger for those who were diagnosed within 10 years of MF/SS diagnosis (OR = 4.12, 95% CI = 1.54 to 11.04 for 2–<5 years before diagnosis; OR = 4.87, 95% CI = 2.15 to 11.02 for 5–<10 years before diagnosis), suggesting possible misdiagnosis of eczema as MF/SS, risk was statisticalltly elevated also for history of eczema beyond 10 years (OR = 1.90, 95% CI = 1.27 to 2.85). An evaluation of individual autoimmune diseases was not permissible due to small numbers. We observed two cases of autoimmune diseases that activate both B and T cells, resulting in a significant increase in MF/SS risk. Other medical conditions, including atopic disorders other than eczema, psoriasis, inflammatory bowel disorders, blood transfusion, HCV infection, oral contraceptive use, and hormone replacement therapy showed weak associations (Table 3).

Table 1. Characteristics of studies included in the InterLymph NHL Subtypes Project*

	Controls	Cases	Total
	No. (%)	No. (%)	No. (%)
Total	17 217 (98.2)	324 (1.8)	17 541
Study			
North America			
British Columbia	845 (4.9)	42 (13.0)	887
Mayo Clinic	1314 (7.6)	9 (2.8)	1323
NCI-SEER	1055 (6.1)	26 (8.0)	1081
Nebraska (newer)	533 (3.1)	7 (2.2)	540
UCSF1	2402 (14.0)	47 (14.5)	2449
UCSF2	457 (2.7)	54 (16.7)	511
University of Rochester	139 (0.8)	2 (0.6)	141
Yale	717 (4.2)	12 (3.7)	729
Europe			
Epilymph	2460 (14.3)	38 (11.7)	2498
Italy multi-center	1771 (10.3)	25 (7.7)	1796
Italy (Aviano-Naples)	504 (2.9)	2 (0.6)	506
SCALE	3187 (18.5)	41 (12.7)	3228
United Kingdom	1139 (6.6)	15 (4.6)	1154
Australia			
New South Wales	694 (4.0)	4 (1.2)	698
Region			
North America	7462 (43.3)	199 (61.4)	7661
Northern Europe	5820 (33.8)	65 (20.1)	5885
Southern Europe	3241 (18.8)	56 (17.3)	3297
Australia	694 (4.0)	4 (1.2)	698
Design			
Population-based	13 846 (80.4)	280 (86.4)	14 126
Hospital-based	3371 (19.6)	44 (13.6)	3415
Age, y			
<30	993 (5.8)	8 (2.5)	1001
30–39	1686 (9.8)	33 (10.2)	1719
40–49	2543 (14.8)	57 (17.6)	2600
50–59	3940 (22.9)	90 (27.8)	4030
60–69	4848 (28.2)	83 (25.6)	4931
70–79	2949 (17.1)	47 (14.5)	2996
≥80	258 (1.5)	6 (1.9)	264
Sex			
Male	9240 (53.7)	184 (56.8)	9424
Female	7977 (46.3)	140 (43.2)	8117
Race			
White, non-Hispanic	15 849 (92.1)	271 (83.6)	16 120
Black	329 (1.9)	19 (5.9)	348
Asian	308 (1.8)	22 (6.8)	330
Hispanic	289 (1.7)	7 (2.2)	296
Other/unknown/missing	442 (2.6)	5 (1.5)	447
Socioeconomic status	6170 (35.8)	117 (36.1)	6287
Medium	5292 (30.7)	94 (29.0)	5386
High	5507 (32.0)	109 (33.6)	5616
Other/missing	248 (1.4)	4 (1.2)	252
NHL classification			
World Health Organization	13 044 (75.8)	252 (77.8)	13 296
Working Formulation	4173 (24.2)	72 (22.2)	4245

* NHL = non-Hodgkin Lymphoma; NCI-SEER = National Cancer Institute Surveillance, Epidemiology, and End Results; SCALE = Scandinavian Lymphoma Etiology Study; UCSF = University of California San Francisco.

A family history of multiple myeloma, but not family history of hematologic malignancies overall, or history of other specific lymphohemopoietic cancer, showed an excess risk (OR = 6.17, 95% CI = 2.39 to 15.91, based on six cases).

An elevated risk of MF/SS was associated with several occupations (Table 4), including crop and vegetable farm workers (OR = 2.76, 95% CI = 1.35 to 5.61), painters (OR = 3.42, 95% CI = 1.81 to 6.47), woodworkers (OR = 2.19, 95% CI = 1.19 to 4.03), and general carpenters (OR = 4.50, 95% CI = 1.74 to 11.62). A significant linear trend was observed with years of employment for woodworkers (*P* for trend = .025) but not others (data not shown). None of the other occupations evaluated showed a significant association with MF/SS risk.

Table 2. Associations between lifestyle factors and risk of Mycosis fungoides and Sézary syndrome*

	Controls	Cases	
	No. (%)	No. (%)	OR (95% CI)†
History of alcohol consumption			
Non-drinker	3003 (19.2)	73 (26.3)	1.00 (referent)
Drinker (at least one drink per month)	8289 (52.9)	146 (52.5)	0.80 (0.58 to 1.09)
History of cigarette smoking‡			
No	6997 (42.7)	121 (42.9)	1.00 (referent)
Yes	8451 (51.6)	139 (49.3)	0.97 (0.75 to 1.25)
0–20, y	3090 (18.9)	47 (16.7)	0.86 (0.61 to 1.23)
21–<30, y	1783 (10.9)	27 (9.6)	0.83 (0.54 to 1.28)
30–<40, y	1737 (10.6)	24 (8.5)	0.79 (0.50 to 1.24)
40≥, y	1742 (10.6)	40 (14.2)	1.60 (1.08 to 2.38)
Missing	1023 (6.2)	23 (8.2)	
Physical activity			
None	716 (10.1)	20 (14.7)	1.00 (referent)
Mild	474 (6.7)	14 (10.3)	0.64 (0.29 to 1.40)
Moderate	934 (13.2)	20 (14.7)	0.44 (0.21 to 0.91)
Vigorous	3037 (43.0)	45 (33.1)	0.50 (0.28 to 0.90)
Usual adult BMI, kg/m^2			
15–<18.5	209 (1.4)	5 (1.7)	1.30 (0.50 to 3.39)
18.5–<22.5	2943 (19.9)	47 (15.9)	1.00 (referent)
22.5–<25	3601 (24.4)	59 (20.0)	1.03 (0.69 to 1.52)
25–<30	5220 (35.4)	107 (36.3)	1.25 (0.87 to 1.80)
35–50	2175 (14.7)	55 (18.6)	1.58 (1.04 to 2.41)
Used hair dyes before 1980			
Never hair dye	1406 (14.4)	27 (13.7)	1.00 (referent)
Ever hair dye use <1980	1101 (11.3)	21 (10.7)	1.08 (0.55 to 2.10)
Hair dye use only 1980≥	966 (9.9)	12 (6.1)	0.78 (0.36 to 1.71)
Hair dye use, time period unknown	986 (10.1)	25 (12.7)	0.99 (0.48 to 2.05)
Male	5071 (51.8)	108 (54.8)	
Total sun exposure (h/wk)			
Q1	1508 (18.7)	24 (21.2)	1.00 (referent)
Q2	1594 (19.8)	21 (18.6)	0.83 (0.46 to 1.50)
Q3	1633 (20.3)	21 (18.6)	0.83 (0.45 to 1.51)
Q4	1714 (21.3)	21 (18.6)	0.75 (0.41 to 1.40)

* CI = confidence interval; OR = odds ratio.

† OR (95% CI) adjusted for age, sex, and race.

‡ Smoked longer than 6 months or more than 100 cigarettes in lifetime.

Results from multivariate analysis are presented in Table 5. All statistically significant associations remained except for vigorous leisure time physical activity.

Limiting our analysis to MF cases (n = 271) did not change the results (data not shown). No meaningful inter-study heterogeneity was detected.

Discussion

The results of our pooled analysis of 324 cases and 17 217 controls from 14 case-control studies from Europe, North America,

Table 3. Associations between medical history and risk of Mycosis fungoides and Sézary syndrome*

	Controls	Cases	
	No. (%)	No. (%)	OR (95% CI)†
Blood transfusion			
No	9591 (82.2)	159 (78.7)	1.00 (referent)
Yes	1715 (14.7)	34 (16.8)	1.19 (0.81 to 1.74)
Ever used OC			
No	2164 (28.0)	32 (21.6)	1.00 (referent)
Yes	1392 (18.0)	34 (23.0)	1.65 (0.91 to 3.01)
Male	4044 (52.3)	80 (54.1)	
Ever used HRT			
No	1716 (26.7)	37 (29.6)	1.00 (referent)
Yes	1072 (16.7)	22 (17.6)	1.17 (0.65 to 2.13)
Male	3351 (52.2)	64 (51.2)	
Infection of HCV			
No	6746 (66.8)	128 (73.6)	1.00 (referent)
Yes	152 (1.5)	1 (0.6)	0.47 (0.07 to 3.47)
Missing	3194 (31.6)	45 (25.9)	
Ulcer			
No	11 639 (82.8)	240 (86.3)	1.00 (referent)
Yes	1020 (7.3)	17 (6.1)	0.93 (0.56 to 1.54)
Psoriasis			
No	10 756 (97.4)	158 (95.8)	1.00 (referent)
Yes	256 (2.3)	7 (4.2)	1.94 (0.89 to 4.23)
Inflammatory bowel disorder			
No	14 454 (97.5)	276 (95.2)	1.00 (referent)
Yes	179 (1.2)	7 (2.4)	1.82 (0.83 to 3.99)
Ulcerative colitis			
No	11 886 (97.2)	238 (95.2)	1.00 (referent)
Yes	145 (1.2)	5 (2.0)	1.68 (0.67 to 4.21)
History of autoimmune disease			
No autoimmune disease	16 500 (95.8)	305 (94.1)	1.00 (referent)
B-cell activation	127 (0.7)	2 (0.6)	1.02 (0.25 to 4.17)
T-cell activation	577 (3.4)	15 (4.6)	1.49 (0.87 to 2.55)
Both	13 (0.1)	2 (0.6)	9.82 (2.05 to 47.03)
Any atopic disorder‡			
No	11 285 (65.5)	185 (57.1)	1.00 (referent)
Yes	5690 (33.0)	129 (39.8)	1.25 (0.98 to 1.61)
Allergy§			
No	9254 (68.8)	161 (61.7)	1.00 (referent)
Yes	3338 (24.8)	73 (28.0)	0.91 (0.67 to 1.24)
Food allergy			
No	11 065 (82.2)	178 (68.2)	1.00 (referent)
Yes	972 (7.2)	21 (8.0)	1.04 (0.64 to 1.69)
Asthma			
No	14 140 (82.8)	260 (80.7)	1.00 (referent)
Yes	1441 (8.4)	28 (8.7)	0.99 (0.67 to 1.48)
Hay fever			
No	9198 (64.9)	132 (48.4)	1.00 (referent)
Yes	2740 (19.3)	55 (20.1)	0.90 (0.63 to 1.30)
History of eczema			
No or <2 y before diagnosis	12 157 (84.9)	205 (74.5)	1.00 (referent)
Yes, 2–<5 y before diagnosis	74 (0.5)	5 (1.8)	4.12 (1.54 to 11.04)
Yes, 5–<10 y before diagnosis	92 (0.6)	7 (2.5)	4.87 (2.15 to 11.02)
Yes, 10 y or more before diagnosis	894 (6.2)	30 (10.9)	1.90 (1.27 to 2.85)
Yes, unknown age	343 (2.4)	10 (3.6)	2.04 (1.03 to 4.04)
Missing	751 (5.2)	18 (6.5)	
First degree family history			
Any hematologic malignancy			
No	10 152 (76.1)	202 (72.4)	1.00 (referent)
Yes	581 (4.4)	16 (5.7)	1.16 (0.68 to 1.98)
Multiple myeloma			
No	7671 (74.5)	162 (71.1)	1.00 (referent)
Yes	36 (0.3)	6 (2.6)	6.17 (2.39 to 15.91)

* CI = confidence interval; HCV = hepatitis C virus; HRT = hormone replacement therapy; OC = oral contraceptives; OR = odds ratio.

† OR (95% CI) adjusted for age, sex, and race.

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

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

Table 4. Associations between occupation and risk of Mycosis fungoides and Sézary syndrome*

	Controls	Cases	
	No. (%)	No. (%)	OR (95% CI)†
Baker and miller			
No	11 152 (96.0)	209 (96.8)	1.00 (referent)
Yes	141 (1.2)	4 (1.9)	1.80 (0.65 to 4.95)
Cleaner			
No	10 775 (92.8)	207 (95.8)	1.00 (referent)
Yes	518 (4.5)	6 (2.8)	0.64 (0.28 to 1.46)
Driver			
No	10 467 (90.1)	200 (92.6)	1.00 (referent)
Yes	826 (7.1)	13 (6.0)	0.83 (0.46 to 1.48)
Electrical and electronics worker			
No	10 589 (91.2)	202 (93.5)	1.00 (referent)
Yes	704 (6.1)	11 (5.1)	0.83 (0.44 to 1.54)
Engine mechanic			
No	10 231 (93.9)	196 (96.1)	1.00 (referent)
Yes	345 (3.2)	5 (2.5)	0.74 (0.30 to 1.83)
Ever worked in farming and farm workers any type			
No	9980 (85.9)	185 (85.6)	1.00 (referent)
Yes	1313 (11.3)	28 13.0)	1.45 (0.94 to 2.22)
Crop and vegetable farm worker			
No	9677 (94.5)	156 (93.4)	1.00 (referent)
Yes	226 (2.2)	9 (5.4)	2.76 (1.35 to 5.61)
Hair dresser			
No	11 144 (95.9)	210 (97.2)	1.00 (referent)
Yes	149 (1.3)	3 (1.4)	1.24 (0.39 to 3.95)
General unspecified laborer			
No	10 667 (91.8)	206 (95.4)	1.00 (referent)
Yes	626 (5.4)	7 (3.2)	0.60 (0.28 to 1.29)
Leather worker			
No	8841 (95.0)	164 (95.9)	1.00 (referent)
Yes	147 (1.6)	4 (2.3)	1.93 (0.69 to 5.37)
Meat worker			
No	11 195 (96.4)	210 (97.2)	1.00 (referent)
Yes	98 (0.8)	3 (1.4)	1.76 (0.55 to 5.67)
Medical worker			
No	10 423 (89.7)	198 (91.7)	1.00 (referent)
Yes	870 (7.5)	15 (6.9)	0.89 (0.52 to 1.53)
Metal worker			
No	10 612 (91.4)	206 (95.4)	1.00 (referent)
Yes	681 (5.9)	7 (3.2)	0.58 (0.27 to 1.24)
Painter			
No	11 099 (95.5)	202 (93.5)	1.00 (referent)
Yes	194 (1.7)	11 (5.1)	3.42 (1.81 to 6.47)
Printer			
No	11 075 (95.3)	208 (96.3)	1.00 (referent)
Yes	218 (1.9)	5 (2.3)	1.33 (0.54 to 3.29)
Teacher			
No	10 142 (87.3)	190 (88.0)	1.00 (referent)
Yes	1151 (9.9)	23 (10.6)	1.12 (0.71 to 1.75)
Textile worker			
No	10 552 (90.8)	199 (92.1)	1.00 (referent)
Yes	741(6.4)	14 (6.5)	1.30 (0.73 to 2.32)
Woodworker			
No	10 969 (94.4)	201 (93.1)	1.00 (referent)
Yes	324 (2.8)	12 (5.6)	2.19 (1.19 to 4.03)
General carpenter			
No	10 493 (96.3)	196 (96.1)	1.00 (referent)
Yes	71 (0.7)	5 (2.5)	4.50 (1.74 to 11.62)

(Table continues)

Table 4 (Continued).

* CI = confidence interval; OR = odds ratio.

† OR(95% CI) adjusted for age, sex, and race.

Table 5. Significant assocaitions from multivariate model*

	Controls	Cases	
	No. (%)	No. (%)	OR (95% CI)†
History of cigarette smoking‡			
No	6997 (42.7)	121 (42.9)	1.00 (reference)
1–20, y	3090 (18.9)	47 (16.7)	0.85 (0.60 to 1.21)
21–30, y	1783 (10.9)	27 (9.6)	0.77 (0.50 to 1.19)
30–39, y	1737 (10.6)	24 (8.5)	0.81 (0.51 to 1.28)
40≥, y	1742 (10.6)	40 (14.2)	1.55 (1.04 to 2.31)
Physical activity			
None	716 (10.1)	20 (14.7)	1.00 (reference)
Mild	474 (6.7)	14 (10.3)	0.74 (0.33 to 1.64)
Moderate	934 (13.2)	20 (14.7)	0.46 (0.22 to 0.97)
Vigorous	3037 (43.0)	45 (33.1)	0.58 (0.32 to 1.08)
Usual adult BMI, kg/m^2			
18.5–<22.5	2943 (19.9)	47 (15.9)	1.00 (reference)
15–<18.5	209 (1.4)	5 (1.7)	1.39 (0.53 to 3.70)
22.5–<25	3601 (24.4)	59 (20.0)	1.02 (0.69 to 1.52)
25–<30	5220 (35.4)	107 (36.3)	1.24 (0.86 to 1.78)
30–50	2175 (14.7)	55 (18.6)	1.57 (1.03 to 2.40)
History of autoimmune disease			
No autoimmune disease	16 500 (95.8)	305 (94.1)	1.00 (reference)
B-cell activation	127 (0.7)	2 (0.6)	1.00 (0.24 to 4.13)
T-cell activation	577 (3.4)	15 (4.6)	1.48 (0.86 to 2.53)
Both	13 (0.1)	2 (0.6)	9.45 (1.80 to 49.60)
History of eczema			
No	12 100 (84.6)	202 (73.5)	1.00 (reference)
Yes	1460 (10.2)	55 (20.0)	2.38 (1.73 to 3.29)
Family history of multiple myeloma			
No	7671 (74.5)	162 (71.1)	1.00 (reference)
Yes	36 (0.3)	6 (2.6)	8.49 (3.31 to 21.80)
Crop and vegetable farm workers			
No	9677 (94.5)	156 (93.4)	1.00 (reference)
Yes	226 (2.2)	9 (5.4)	2.37 (1.14 to 4.92)
Painter			
No	11 099 (95.5)	202 (93.5)	1.00 (reference)
Yes	194 (1.7)	11 (5.1)	3.71 (1.94 to 7.07)
Woodworkers			
No	10 969 (94.4)	201 (93.1)	1.00 (reference)
Yes	324 (2.8)	12 (5.6)	2.20 (1.18 to 4.08)
General carpenter			
No	10 493 (96.3)	196 (96.1)	1.00 (reference)
Yes	71 (0.7)	5 (2.5)	4.07 (1.54 to 10.75)

* CI = confidence interval; OR = odds ratio.

† OR (95% CI) adjusted for age, sex, race, and all other variables listed in the table.

‡ Smoked longer than 6 months or more than 100 cigarettes in lifetime.

and Australia, suggest that subjects with a positive family history of multiple myeloma and subjects working in crop and vegetable farms, or as painters, carpenters or woodworkers, might be at an increased risk of MF/SS. A history of eczema for more than 10 years before MF/SS diagnosis also increased risk. Among personal and lifestyle risk factors, only obesity and prolonged cigarette smoking seem to convey an increased risk, while a moderate/vigorous leisure time physical activity might be protective. As both MF and SS are rare, few results have previously been published and are available for comparison with our findings.

Chronic exposure to cigarette smoke has been associated with decreased immune responsiveness, particularly for T cells, in both human and animal studies (25), which would suggest a potential link to decreased immune surveillance and increased lymphoma risk. In a previous pooled InterLymph study, heavy smoking was associated with an increased risk of follicular lymphoma but not other NHL subtypes, including MF (26). In the European multicenter study of MF, a linear increase in MF risk with increasing pack-years of smoking was observed, although the trend was not statistically significant (27). In the analyses presented here, a significant association was observed among individuals who had smoked cigarettes for 40 years or more, but no dose–response was observed with increasing duration.

Obesity promotes a state of low-grade chronic inflammation and increased production of proinflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor-α, IL-1b, and leptin (28). These cytokines can deregulate T- and B-cell responses and enhance B-cell proliferation and survival, factors that may provide a milieu that favors lymphomagenesis (29). In our analysis, a BMI greater than or equal to 30 kg/m^2 was associated with an increased risk of MF/SS, although we were unable to support with statistical significance the observed linear increase in risk by increasing BMI. A similar finding was reported for diffuse large B-cell lymphoma in a previous InterLymph study of NHL overall and common NHL subtypes; however, MF/SS was not analyzed as a separate outcome in that study (30).

Moderate physical activity may improve immune function and it may therefore protect against NHL and possibly MF/SS (31). In our study we found that, compared with people who were not engaged in leisure-time physical activity, those who engaged in moderate and vigorous physical activity experienced a reduced risk of MF/SS. However, the decrease in MF/SS risk by increasing level of physical activity was not linear, and the multivariate analysis partially weakened the inverse association. Previous reports suggest that moderate exercise may reduce NHL risk (32,33). More research in this area is warranted.

In agreement with a previous InterLymph study (13), we found that a previous medical history of eczema was associated with an increased risk of MF/SS, which appeared to be stronger for those who were diagnosed within 10 years of MF/SS diagnosis. Such a pattern might suggest the possibility that early MF may be mistaken for eczema in some cases. Alternatively, the association with eczema may be an indicator of eczema as an early disease rather than a risk factor as it often goes undiagnosed for years. However, the risk remained significantly elevated for those who were diagnosed more than 10 years before MF/SS diagnosis. Eczema is a form of chronic dermatitis which is known to have a pathogenetic association with early stages of MF (34). Specific autoimmune diseases were rare and no analysis of their associations with MF/SS risk was feasible; after categorizing autoimmune diseases by whether B or T cells were activated, no association was observed. However, two cases of autoimmune diseases that activate both B and T cells were observed, resulting in an elevated MF/SS risk. B cell activating diseases included Hashimoto thyroiditis, hemolytic anemia, myasthenia gravis, pernicious anemia, rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus. T cell activating diseases included celiac disease, immune thrombocytopenic purpura, inflammatory bowel disorder (Crohn's disease, ulcerative colitis), multiple sclerosis, polymyositis or dermatomyositis, psoriasis, sarcoidosis, systemic sclerosis or scleroderma, and type 1 diabetes.

A role for genetic susceptibility in MF/SS is supported by the accumulating evidence of common genetic variations altering MF risk (35,36). In our study, persons with a family history of multiple myeloma had an excess risk of MF/SS, but no association was found with family history of any hematologic malignancy. In a previous pooled InterLymph analysis, risk of specific NHL subtypes, including T-cell lymphomas (MF/SS were not separately evaluated), were elevated among subjects who reported a family history of hematologic malignancies in first-degree relatives, particularly multiple myeloma in males (37). However, it is also possible that since multiple myeloma and MF are increased in blacks (37), this may confound the association.

The evaluation of occupational risk factors showed that crop and vegetable farm workers, painters, woodworkers and carpenters experienced an increased risk of MF/SS. Although we did not examine specific occupational exposures, our findings are consistent with the results of other studies that examined exposures potentially encountered in these occupations. In a European case–control study, occupational exposures to the broad category of aromatic and/or halogenated hydrocarbons, which are widely used as solvents, and to pesticides in general were identified as potential risk factors for MF (10). An excess risk of NHL among farmers and agricultural workers has been repeatedly reported, suggesting a potential link with farming exposures including pesticides (38,39). Among the most commonly used agrochemicals, organophosphate insecticides were associated with an increased risk in the European Epilymph study, limited to the chronic lymphocytic leukemia subtype (40). Other occupations previously associated with an increase in MF risk include different manufacturing industries, such as petrochemical, textile, and various metal industries (41–43). Painters and woodworkers may also be exposed to solvents in paint thinners and paint and grease removers, including benzene and trichloroethylene previously associated with increased risk of other NHL subtypes in prior reports from included studies (44,45). Other exposures possibly related to the excess risk we observed for these occupations include chlorophenols, wood dust, and molds (Cocco P, unpublished data). Our results suggest that these and other potentially harmful exposures should be explored in greater detail in future investigations using advanced occupational exposure assessment methods.

Although this is the largest study to date that examines numerous putative risk factors in relation to MF/SS, the small number of subjects was still a limitation. All cases were histologically confirmed, but centralized review of all cases by a team of study pathologists was not feasible, and thus some misclassification may be present. As multiple hypotheses have been tested and a number of comparisons have been made, chance findings cannot be ruled out.

Since only 13 SS cases were included in this study, we were unable to examine associations specific to SS; therefore, the observed associations were predominantly driven by MF and may not apply to SS. Another limitation is related to the number of comparisons we made, which might have generated several positive findings as the sole result of chance. However, negative findings might have been missed as the study size is insufficient to detect weaker associations. In conclusion, our pooled analysis of lifestyle factors, medical history, and occupation and MF/SS suggests potential positive associations with elevated BMI, long-term cigarette smoking, eczema, and family history of multiple myeloma, and a potential negative association with moderate leisure time physical activity. Our findings for farming and other occupations point to avenues for additional research to identify specific occupational exposures that may be responsible for these associations. Future research is warranted to confirm these findings in prospectively collected data and in other populations.

References

1. Bradford PT, Devesa SS, Anderson WF, Toro JR. Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood*. 2009;113(21):5064–5073.
2. Imam MH, Shenoy PJ, Flowers CR, Phillips A, Lechowicz MJ. Incidence and survival patterns of cutaneous T-cell lymphomas in the United States. *Leuk Lymphoma*. 2013;54(4):752–759.
3. Saunes M, Nilsen TI, Johannesen TB. Incidence of primary cutaneous T-cell lymphoma in Norway. *Br J Dermatol*. 2009;160(2):376–379.
4. Ishihara K, Saida T, Otsuka F, Yamazaki N. Statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. *Int J Clin Oncol*. 2008;13(1):33–41.
5. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 3rd ed. Lyon, France: IARC Press; 2001.
6. Agar NS, Wedgeworth E, Crichton S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. *J Clin Oncol*. 2010;28(31):4730–4739.
7. Talpur R, Singh L, Daulat S, et al. Long-term outcomes of 1,263 patients with mycosis fungoides and Sezary syndrome from 1982 to 2009. *Clin Cancer Res*. 2012;18(18):5051–5060.
8. Criscione VD, Weinstock MA. Incidence of cutaneous T-cell lymphoma in the United States, 1973-2002. *Arch Dermatol*. 2007;143(7):854–859.
9. Whittemore AS, Holly EA, Lee IM, et al. Mycosis fungoides in relation to environmental exposures and immune response: a case-control study. *J Natl Cancer Inst*. 1989;81(20):1560–1567.
10. Morales-Suarez-Varela MM, Olsen J, Johansen P, et al. Occupational exposures and mycosis fungoides. A European multicentre case-control study (Europe). *Cancer Causes Control*. 2005;16(10):1253–1259.
11. Linet MS, McLaughlin JK, Fraumeni JF Jr, Malker HS, Weiner JA, Ericsson JL. Mycosis fungoides and occupation in Sweden. *J Natl Cancer Inst*. 1989;81(23):1842–1843.
12. Morales-Suarez-Varela MM, Olsen J, Villeneuve S, et al. Occupational exposure to chlorinated and petroleum solvents and mycosis fungoides. *J Occup Environ Med*. 2013;55(8):924–31.
13. Vajdic CM, Falster MO, de Sanjose S, et al. Atopic disease and risk of non-Hodgkin lymphoma: an InterLymph pooled analysis. *Cancer Res*. 2009;69(16):6482–6489.
14. Morales-Suarez-Varela MM, Olsen J, Johansen P, et al. Occupational sun exposure and mycosis fungoides: a European multicenter case-control study. *J Occup Environ Med*. 2006;48(4):390–393.
15. van Leeuwen MT, Turner JJ, Falster MO, et al. Latitude gradients for lymphoid neoplasm subtypes in Australia support an association with ultraviolet radiation exposure. *Int J Cancer*;133(4):944–951.
16. Gupta RK, Ramble J, Tong CY, Whittaker S, MacMahon E. Cytomegalovirus seroprevalence is not higher in patients with mycosis fungoides/Sezary syndrome. *Blood*. 2006;107(3):1241–1242.
17. Tothova SM, Bonin S, Trevisan G, Stanta G. Mycosis fungoides: is it a Borrelia burgdorferi-associated disease? *Br J Cancer*. 2006;94(6):879–883.
18. Trento E, Castilletti C, Ferraro C, et al. Human herpesvirus 8 infection in patients with cutaneous lymphoproliferative diseases. *Arch Dermatol*. 2005;141(10):1235–42.
19. Herne KL, Talpur R, Breuer-McHam J, Champlin R, Duvic M. Cytomegalovirus seropositivity is significantly associated with mycosis fungoides and Sézary syndrome. *Blood*. 2003;101(6):2132–2136.
20. de Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. *Clin Gastroenterol Hepatol*. 2008;6(4):451–8.
21. Swerdlow SH, Campo E, Harris NL, et al., eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008.
22. Morton LM, Turner JJ, Cerhan JR, et al. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). *Blood*. 2007;110(2):695–708.
23. Turner JJ, Morton LM, Linet MS, et al. InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions. *Blood*. 2010;116(20):e90–e98.
24. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
25. Sopori ML, Kozak W. Immunomodulatory effects of cigarette smoke. *J Neuroimmunol*. 1998;83(1–2):148–156.
26. Morton LM, Hartge P, Holford TR, et al. Cigarette smoking and risk of non-Hodgkin lymphoma: a pooled analysis from the International Lymphoma Epidemiology Consortium (InterLymph). *Cancer Epidemiol Biomarkers Prev*. 2005;14(4):925–33.
27. Morales Suarez-Varela MM, Olsen J, Kaerlev L, et al. Are alcohol intake and smoking associated with mycosis fungoides? A European multicentre case-control study. *Eur J Cancer*. 2001;37(3):392–7.
28. Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest*. 2011;121(6):2111–2117.
29. Harris AW, Strasser A, Elefanty AG, Bath ML, Cory S. Deregulation of cell survival in lymphomagenesis. *Leukemia*. 1997;11(suppl 3):383–384.
30. Willett EV, Morton LM, Hartge P, et al. Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. *Int J Cancer*. 2008;122(9):2062–70.
31. Ballard-Barbash R, Friedenreich C, Slattery M, Thune L. Obesity and body composition. In: Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention*. 3rd ed. New York, NY: Oxford University Press; 2006.
32. Cerhan JR, Bernstein L, Severson RK, et al. Anthropometrics, physical activity, related medical conditions, and the risk of non-hodgkin lymphoma. *Cancer Causes Control*. 2005;16(10):1203–1214.
33. Pan SY, Mao Y, Ugnat AM. Physical activity, obesity, energy intake, and the risk of non-Hodgkin's lymphoma: a population-based case-control study. *Am J Epidemiol*. 2005;162(12):1162–1173.
34. Burg G, Dummer R, Haeffner A, Kempf W, Kadin M. From inflammation to neoplasia: mycosis fungoides evolves from reactive inflammatory conditions (lymphoid infiltrates) transforming into neoplastic plaques and tumors. *Arch Dermatol*. 2001;137(7):949–952.
35. Bellei B, Cota C, Amantea A, Muscardin L, Picardo M. Association of p53 Arg72Pro polymorphism and beta-catenin accumulation in mycosis fungoides. *Br J Dermatol*. 2006;155(6):1223–1229.
36. Skibola CF, Bracci PM, Nieters A, et al. Tumor necrosis factor (TNF) and lymphotoxin-alpha (LTA) polymorphisms and risk of non-Hodgkin lymphoma in the InterLymph Consortium. *Am J Epidemiol*. 2010;171(3):267–276.
37. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood*. 2007;109(8):3479–3488.

38. Alavanja MC, Bonner MR. Occupational pesticide exposures and cancer risk: a review. *J Toxicol Environ Health B Crit Rev*. 2012;15(4):238–263.
39. Dich J, Zahm SH, Hanberg A, Adami HO. Pesticides and cancer. *Cancer Causes Control*. 1997;8(3):420–443.
40. Cocco P, Satta G, Dubois S, et al. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. *Occup Environ Med*. 2013;70(2):91–98.
41. Kuzel TM, Roenigk HH Jr, Rosen ST. Mycosis fungoides and the Sézary syndrome: a review of pathogenesis, diagnosis, and therapy. *J Clin Oncol*. 1991;9(7):1298–1313.
42. Linet MS, McLaughlin JK, Malker HS, et al. Occupation and hematopoietic and lymphoproliferative malignancies among women: a linked registry study. *J Occup Med*. 1994;36(11):1187–1198.
43. Tuyp E, Burgoyne A, Aitchison T, MacKie R. A case-control study of possible causative factors in mycosis fungoides. *Arch Dermatol*. 1987;123(2):196–200.
44. Cocco P, t'Mannetje A, Fadda D, et al. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. *Occup Environ Med*. 2010;67(5):341–7.
45. Cocco P, Vermeulen R, Flore V, et al. Occupational exposure to trichloroethylene and risk of non-Hodgkin lymphoma and its major subtypes: a pooled InterLlymph analysis. *Occup Environ Med*. 2013;70(11):795–802.

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Affiliations of authors: Department of Health Studies, University of Chicago, Chicago, IL (BA-K); Department of Public Health, Clinical and Molecular Medicine, Occupational Health Section, University of Cagliari, Cagliari, Italy (PC); Dipartimento di Epidimologia, IRCCS- Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy, Community Health, University of Milan, Milan, Italy (CLV); Health Sciences Practice, Exponent, Inc., Menlo Park, CA, Department of Health Research and Policy, Stanford University, Stanford, CA (ETC); Prince of Wales Clinical School, University of New South Wales, Sydney, Australia (CMV); Department of Dermatology, Boston University, Boston, MA, Roger Williams Medical Center, Providence, RI (MEK); Cancer Control Research, BC Cancer Agency, Vancouver, BC, Canada, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada (JJS); Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health Bethesda, MD (LMM, JNS); Epidemiology and Cancer Statistics Group, Department of Health Sciences, University of York, York, UK (EVK); Biostatistics Center, Massachusetts General Hospital, Boston, MA (CK); Department of Laboratory Medicine and Pathology, Mayo Clinic Cancer Center, Rochester, MN (ALF); Division of Cancer Etiology, Department of Population Sciences, Beckman Research Institute of the City of Hope, Duarte, CA (SSW); Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT (YZ).