

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

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Background	Accounting for 10%–15% of all non-Hodgkin lymphomas in Western populations, peripheral T-cell lymphomas (PTCL) are the most common T-cell lymphoma but little is known about their etiology. Our aim was to identify etiologic risk factors for PTCL overall, and for specific PTCL subtypes, by analyzing data from 15 epidemiologic studies participating in the InterLymph Consortium.
Methods	A pooled analysis of individual-level data for 584 histologically confirmed PTCL cases and 15912 controls from 15 case–control studies conducted in Europe, North America, and Australia was undertaken. Data collected from questionnaires were harmonized to permit evaluation of a broad range of potential risk factors. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression.
Results	Risk factors associated with increased overall PTCL risk with a <i>P</i> value less than .05 included: a family history of hematologic malignancies (OR = 1.92, 95% CI = 1.30 to 2.84); celiac disease (OR = 17.8, 95% CI = 8.61 to 36.79); eczema (OR = 1.41, 95% CI = 1.07 to 1.85); psoriasis (OR = 1.97, 95% CI = 1.17 to 3.32); smoking 40 or more years (OR = 1.92, 95% CI = 1.41 to 2.62); and employment as a textile worker (ever) (OR = 1.58, 95% CI = 1.05 to 2.38) and electrical fitter (ever) (OR = 2.89, 95% CI = 1.41 to 5.95). Exposures associated with reduced overall PTCL risk included a personal history of allergies (OR = 0.69, 95% CI = 0.54 to 0.87), alcohol consumption (ever) (OR = 0.64, 95% CI = 0.49 to 0.82), and having ever lived or worked on a farm (OR = 0.72, 95% CI = 0.55% to 0.95%). We also observed the well-established risk elevation for enteropathy-type PTCL among those with celiac disease in our data.
Conclusions	Our pooled analyses identified a number of new potential risk factors for PTCL and require further validation in independent series.
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Accounting for 10%–15% of all non-Hodgkin lymphomas (NHL) in Western populations (1), peripheral T-cell lymphomas (PTCL) are the most common T-cell lymphomas but are still relatively rare. The incidence of PTCLs rises monotonically with age but remains less than 1 per 100 000 according to the US Surveillance, Epidemiology, and End Results registry (2). PTCL incidence rates are higher among black compared with white populations in the United States, and higher in men compared with women, but incidence rose between 1997 and 2006 in all race groups and in both males and females. PTCL itself comprises a diverse group of diseases with largely aggressive behavior and poor prognosis. Nodal PTCLs include PTCL not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL), and angioimmunoblastic lymphoma, whereas the more aggressive extranodal PTCLs include natural killer or nasal type, enteropathy-associated PTCL, hepatosplenic PTCL, and subcutaneous panniculitis-like PTCL.

The current World Health Organization classification system (3) recognizes 13 PTCL subtypes; however, some of the major PTCL subtypes, including PTCL-NOS and ALCL, are themselves thought to comprise heterogeneous entities (4–11).

Few risk factors have been identified for PTCL largely due to its low incidence, but some risk factors and molecular characteristics specific to individual PTCL subtypes have been identified (2). For example, infection with human T-cell lymphotropic virus-1, which is endemic in southern Japan and Jamaica, is associated with adult T-cell leukemia or lymphoma (1), and infection with Epstein–Barr virus has been implicated in the etiology of natural killer and T-cell lymphoma, nasal type (12). The chromosomal translocation t(2;5)(p23;q35), which results in the fusion protein NPM-ALK (2), is found specifically in ALCL. A possible link between breast implants and ALCL has also been reported (13–18). While these risk factors do not explain the majority of PTCLs that arise, they do suggest that PTCL subtypes may have distinct etiologies.

Large consortia can contribute substantially toward furthering our understanding of disease etiology, particularly by amassing a sufficient number of cases to detect modest but important associations. As part of the International Lymphoma Epidemiology Consortium (InterLymph) NHL Subtypes Project, we present results from a pooled analysis of 584 PTCL cases and 15 912 controls from 15 participating case-control studies conducted in Europe, North America, and Australia, to investigate the associations between family history, medical history, lifestyle and occupational risk factors, and risk of PTCL and its major subtypes.

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 PTCL, 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 and AIDS. Contributing studies were approved by the local ethics review committees and all participants provided written or verbal informed consent before interview.

PTCL Subtype Ascertainment and Harmonization

Cases were classified according to the World Health Organization classification (3,19) using guidelines from the InterLymph Pathology Working Group (20,21). 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 also reviewed by an interdisciplinary team of pathologists and epidemiologists, who then applied the World Health Organization classification guidelines.

Because PTCL risk factors may differ by site of involvement, we further classified cases accordingly. In most studies, the primary site of lymphoma was recorded, where known, irrespective of disease stage. Indeed, for some PTCL subtypes, site is a diagnostic criterion. Initially, lymphoma sites were categorized as nodal, extranodal lymphatic (Waldeyer's ring, thymus, or spleen), or extranodal extralymphatic (22). For some NHL subtypes, specific primary sites (eg, skin, gastrointestinal tract) were also recorded. Leukemias were classified as systemic by definition. Similarly, cases with widespread disease, no known primary site, or a primary site listed as bone marrow, blood, or cerebrospinal fluid, or in which the subtype was not site-specific by definition, also were classified as systemic.

Risk Factor Ascertainment and Harmonization

Each study collected data on putative NHL risk factors in a standardized, structured format by either in-person or telephone interviews (typically computer-assisted) or self-reported questionnaires. Risk factors selected for inclusion in these analyses were family history, medical history, and lifestyle and occupational risk factors with data from at least four studies. To minimize reverse causality, medical conditions, and atopic conditions reported at least 2 years before

NHL diagnosis were excluded. Details of the data harmonization rules are provided elsewhere in this issue.

Statistical Analysis

Risk of PTCL was examined for each exposure variable using logistic regression models adjusted for age, race and ethnicity, sex, and study ("basic model"). Statistical significance was evaluated by the likelihood ratio test, comparing models with and without the exposure variable of interest, with *P* value less than .05 identifying putatively significant risk factors. Individuals with missing data for the exposure variable of interest were excluded from that analysis. To evaluate effect heterogeneity between studies, we performed a separate logistic regression analysis within each study and then quantified the variability of the coefficients using the *H* statistic, adapting the definition by Higgins and Thompson (23) to categorical variables.

We examined the relationship between case and 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, sex, race and ethnicity, region, study, study design (ie, population-based vs hospital- or clinic-based), or other putative risk factors identified in the analysis. As described in the "Rationale and Design" paper in this issue, forest plots illustrating the results from the stratified analyses were reviewed to identify possible modifiers of the effect of an exposure variable of interest. This approach permitted us to evaluate whether odds ratios (ORs) were consistent by strata and visually observe whether confidence intervals (CIs) overlapped. Because no differences were observed by strata, we did not further calculate differences in strata using more formal statistical methods. To account for other potential confounders, we conducted three analyses. Firstly, we evaluated the risk estimate for each putative risk factor in a series of models that adjusted for one other putative risk factor individually, as well as age, race and ethnicity, sex, and study. Secondly, we conducted a single logistic regression model including all putative risk factors and a separate missing category for each variable to ensure that the whole study population was included in the analysis (ie, no individuals were dropped due to missing data). Although creating a separate "missing" category to accommodate missing values in our models can potentially introduce bias (24), in practice, this method provides similar results to those from more modern methods such as multiple imputation (25). Moreover, as only a subset of studies collected any given covariate, we would have needed to use a multilevel imputation method (26) and we were not confident that those methods had been fully evaluated in repeated application. Finally, we conducted a forward step-wise logistic regression with all putative risk factors, adjusting for age, sex, race and ethnicity, and study ("final model"). Forward step-wise logistic regression was conducted to construct the most parsimonious model of independent variables from the large total number of covariates and correlated variables.

Controls for most original studies were frequency matched by age and sex to NHL cases, rather than just PTCL. We therefore conducted sensitivity analyses using a subset of controls specifically frequency matched by age and sex to PTCL cases. The results from these sensitivity analyses were very similar to the results obtained using the full set of controls; thus, to increase statistical power, we

retained the full set of controls in the main analyses. All analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

Results

In all, 584 cases of PTCL and 15912 controls, enrolled in 15 participating InterLymph Consortium case-control studies from North America, Europe, and Australia (Table 1), were included in the analyses. The study population was largely non-Hispanic white (88% of cases, 94% of controls). Of PTCL cases, 59% were men; age distribution was similar between cases and controls, with a median of 55 years. Major PTCL subtypes further evaluated as distinct entities were PTCL NOS ($n = 234$), ALCL ($n = 164$), and angioimmunoblastic lymphoma ($n = 81$). Rarer PTCL subtypes with sample size less than 50 were primary cutaneous ALCL ($n = 45$), enteropathy-type PTCL ($n = 23$), and cutaneous PTCL NOS ($n = 27$), for which results are shown in Supplementary Tables 2–4 (available online). These results warrant cautious interpretation due to the small sample size for each of these subtypes. Analyses were not conducted for subcutaneous panniculitis-like or hepatosplenic PTCL as they had only seven and three cases, respectively. Mycosis fungoides and Sézary syndrome were evaluated and reported separately in this issue. Of all potential risk factors evaluated and described in a separate article in this issue, our presentation is limited to those found to be associated with PTCL or PTCL subtypes with P values less than .05. No effect modification by demographic or putative risk factors was identified, so results are shown without stratification. Further, no significant heterogeneity by study was noted based on the H statistic, and results are thus not stratified by study or study type. Results from both the basic and final models are shown.

Medical History

Participants reporting a history of celiac disease had an 18-fold increase in risk (OR = 17.80, 95% CI = 8.61 to 36.79) for PTCL overall (Table 2). This association was also significant for several PTCL subtypes, including PTCL-NOS (OR = 8.66, 95% CI = 1.97 to 38.1) (Table 3) and ALCL (OR = 16.59, 95% CI = 3.27 to 84.31) (Table 4). Although based on small numbers, associations were also observed between personal history of celiac disease and primary cutaneous ALCL (OR = 39.9; Supplementary Table 2, available online). Additionally, although there were only 23 cases with enteropathy-type PTCL, the established risk with celiac disease was detected in our study population (OR = 215, 95% CI = 44 to 1041) (Supplementary Table 4, available online).

A personal history of allergies was associated with a decreased risk for PTCL (OR = 0.69, 95% CI = 0.54 to 0.87) and largely driven by the significant association with PTCL-NOS (OR = 0.67, 95% CI = 0.46 to 0.98) (Tables 2 and 3).

A personal history of eczema was associated with a modest increase in PTCL risk (OR = 1.41, 95% CI = 1.07 to 1.85) (Table 2), especially for ALCL at ages less than 30 years (Supplementary Table 1, available online). A personal history of psoriasis was associated with increased risk of PTCL (OR = 1.97, 95% CI = 1.17 to 3.32) (Table 2), PTCL-NOS (OR = 2.41, 95% CI = 1.15 to 5.04) (Table 3), and ALCL, though the latter association was significant

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

	Controls	Cases
	N (%)	N (%)
Total	15912 (96.5)	584 (3.5)
Study		
North America		
British Columbia	846 (5.3)	33 (5.7)
Los Angeles	376 (2.4)	1 (0.2)
Mayo Clinic	1314 (8.3)	32 (5.5)
NCI-SEER	1056 (6.6)	55 (9.4)
Nebraska (newer)	534 (3.3)	12 (2.1)
UCSF2	457 (2.9)	78 (13.2)
University of Rochester	138 (0.9)	8 (1.4)
Yale	718 (4.5)	19 (3.3)
Europe		
Engela	723 (4.5)	18 (3.1)
EpiLymph	2461 (15.5)	78 (13.4)
Italy multicenter	1771 (11.1)	55 (9.4)
Italy (Aviano-Naples)	503 (3.2)	9 (1.5)
SCALE	3187 (20.0)	121 (20.7)
United Kingdom	1139 (7.2)	50 (8.6)
Australia		
New South Wales	693 (4.4)	16 (2.7)
Region		
North America	5435 (34.2)	237 (40.6)
Northern Europe	6542 (41.1)	243 (41.6)
Southern Europe	3241 (20.4)	88 (15.1)
Australia	694 (4.4)	16 (2.7)
Design		
Population-based	11819 (74.3)	472 (80.8)
Hospital-based	4093 (25.7)	112 (19.2)
Age, y		
<30	941 (5.9)	48 (8.2)
30–39	1365 (8.6)	61 (10.4)
40–49	2296 (14.4)	99 (17.0)
50–59	3784 (23.8)	125 (21.4)
60–69	4513 (28.4)	156 (26.7)
70–79	2752 (17.3)	85 (14.6)
≥80	258 (1.6)	7 (1.2)
Missing	0 (0.0)	3 (0.5)
Sex		
Male	8302 (52.2)	347 (59.4)
Female	7610 (47.8)	237 (40.6)
Race		
White, non-Hispanic	14908 (93.7)	512 (87.7)
Black	219 (1.4)	13 (2.2)
Asian	202 (1.3)	23 (3.9)
Hispanic	180 (1.1)	14 (2.4)
Other/unknown/missing	403 (2.5)	22 (3.8)
SES		
Low	5835 (36.7)	204 (34.9)
Medium	5087 (32.0)	182 (31.2)
High	4743 (29.8)	183 (31.3)
Other/missing	247 (1.6)	15 (2.6)
NHL subtype		
World Health Organization	—	528 (90.4)
Working Formulation	—	56 (9.6)
PTCL subtype		
PTCL-NOS	—	234 (40.1)
Enteropathy type	—	23 (3.9)
Cutaneous PTCL-NOS	—	27 (4.6)
ALCL	—	164 (28.1)
Angioimmunoblastic	—	81 (13.9)
Subcutaneous panniculitis-like	—	7 (1.2)

(Table continues)

Table 1 (Continued).

	Controls	Cases
	No. (%)	No. (%)
Hepatosplenic	—	3 (0.5)
Primary cutaneous ALCL	—	45 (7.7)
PTCL site		
Not collected	—	131 (22.4)
Nodal	—	214 (36.6)
Extranodal: lymphatic (spleen)	—	3 (0.5)
Extranodal: lymphatic (other)	—	10 (1.7)
Extranodal: nonlymphatic (stomach)	—	5 (0.9)
Extranodal: nonlymphatic (skin)	—	105 (18.0)
Extranodal: nonlymphatic (CNS)	—	1 (0.2)
Extranodal: nonlymphatic (mediastinum)	—	3 (0.5)
Extranodal: nonlymphatic (parotid or salivary gland)	—	1 (0.2)
Extranodal: nonlymphatic (intestine/colon/rectum)	—	34 (5.8)
Extranodal: nonlymphatic (all other specified)	—	33 (5.7)
Extranodal: nonlymphatic (site unknown)	—	15 (2.6)
Systemic	—	23 (3.9)
Unknown/unclassifiable	—	6 (1.0)

*ALCL = anaplastic large cell lymphoma; CNS = central nervous system; NCI-SEER = National Cancer Institute-Surveillance, Epidemiology, and End Results; NHL = non-Hodgkin lymphoma; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified; SCALE = Scandinavian Lymphoma Etiology Study; SES = socioeconomic status; UCSF = University of California San Francisco.

only for ALCL diagnosed at ages greater than or equal to 30 years (Supplementary Table 1, available online).

Although we could not directly evaluate *Helicobacter pylori* infection, an established risk factor for enteropathy-type PTCL, having had a peptic ulcer was associated with an increased risk of enteropathy-type PTCL (OR = 8.69, 95% CI = 2.54 to 29.78) (Supplementary Table 4, available online).

Lifestyle Factors

A 1.92-fold increased risk of PTCL overall (OR = 1.92, 95% CI = 1.41 to 2.62) was observed among those who smoked cigarettes for 40 or more years, compared with nonsmokers (Table 2). Increased risk of PTCL-NOS and ALCL was also observed in association with longer duration of cigarette smoking, with a duration risk trend ($P < .001$) (Tables 3 and 4). Of the rarer PTCL subtypes, evidence of increased risk for cigarette smoking was also suggestive for primary cutaneous ALCL (Supplementary Table 2, available online).

Alcohol consumption, defined as at least one alcoholic drink per month, was associated with reduced PTCL risk (OR = 0.64, 95% CI = 0.49 to 0.82) (Table 2). The association was specifically detected for PTCL-NOS (Table 3).

The highest versus lowest quartile of recreational sun exposure was associated with a 48% decrease in ALCL risk (95% CI = 0.26 to 0.88) (Table 4).

Family History

A first-degree family history of any hematologic malignancy was associated with 1.92-fold increased risk of PTCL overall (95%

CI = 1.30 to 2.84) (Table 2). By PTCL subtypes, significant associations for family history of hematologic malignancies were also observed for PTCL-NOS (OR = 1.92, 95% CI = 1.05 to 3.49) (Table 3) and angioimmunoblastic lymphoma (OR = 2.55, 95% CI = 1.10 to 5.89) (Table 5).

Occupational Factors

A modest risk increase for PTCL overall was observed for ever employment as a textile worker (OR = 1.58, 95% CI = 1.05 to 2.38), and though based on small numbers, a nearly threefold increase in risk of PTCL was observed for those having the occupation of electrical fitter during their lifetime (OR = 2.89, 95% CI = 1.41 to 5.95) (Table 2). Both occupational groups (textile workers and electrical fitters) had significantly increased risk of ALCL (Table 4); electrical fitters also had increased risk for angioimmunoblastic lymphoma (OR = 5.45, 95% CI = 1.20 to 24.7) (Table 5). Of the rarer PTCL subtypes, PTCL enteropathy-type lymphoma was also positively associated with textile work (Supplementary Table 4, available online). In contrast, those reporting having ever lived or worked on a farm had reduced risk for PTCL (OR = 0.72, 95% CI = 0.55 to 0.95) (Table 2).

Discussion

This study is the first systematic effort to identify risk factors specific to PTCL and its subtypes. Our results are consistent with previously reported risk factors, including family history of hematologic malignancies and personal history of autoimmune conditions and celiac disease and eczema. Importantly, we identified several new potential risk factors, including long-term smoking and some occupations, such as electrical fitters and textile workers, though these results require replication in future efforts before any conclusion can be drawn. In addition, several factors were associated with a reduction in PTCL risk, including a history of alcohol consumption (though duration was not consistently associated) and a personal history of allergies. Although the numbers of cases for some PTCL subtype were modest, we were able to confirm the well-established association between celiac disease and enteropathy-type PTCL and indirectly support the association between *H. pylori* (via history of peptic ulcer) and enteropathy-type PTCL.

Prior to these analyses, the only established risk factors for T-cell lymphomas were family history of hematologic malignancies (27) and history of celiac disease (28). In particular, there has been a longstanding association between celiac disease and enteropathy-type PTCL (29) which may arise as a result of clonal proliferation of phenotypically abnormal intraepithelial lymphocytes associated with the loss of CD8 expression and increased interleukin-15 expression (30,31). The results from this study extend those associations to PTCL and quantify the relative risks, and also demonstrate that a family history of any lymphoid malignancy is associated with increased risk for PTCL overall, PTCL-NOS, and angioimmunoblastic lymphoma.

The role of atopic conditions, such as allergies and asthma, in lymphoma etiology has been the subject of much debate. In simplistic terms, it has been hypothesized that inflammatory responses resulting from a Th1 response increase lymphoma risk, whereas a Th2 immune response induced by atopic conditions reduces NHL

Table 2. Peripheral T-cell lymphoma overall: basic model (adjusted for age, race, sex, and study) and final model (adjusted for age, race, sex, study, and all other variables in the model)*

	Controls, N (%)	Cases, N (%)	Basic OR (95% CI)	P	Final OR (95% CI)	P
Medical history						
Celiac disease						
No	10 501 (97.9)	386 (93.7)	1.00 (referent)	<.001	1.00 (referent)	<.001
Yes	26 (0.20)	12 (2.90)	15.5 (7.60 to 31.6)		17.80 (8.61 to 36.79)	
Allergy						
No	9852 (69.5)	371 (67.8)	1.00 (referent)	.01	1.00 (referent)	.002
Yes	3458 (24.4)	124 (22.7)	0.75 (0.60 to 0.93)		0.69 (0.54 to 0.87)	
Eczema						
No	13 108 (85.1)	466 (81.0)	1.00 (referent)	.09	1.00 (referent)	.02
Yes	1543 (10.0)	71 (12.3)	1.27 (0.97 to 1.65)		1.41 (1.07 to 1.85)	
Psoriasis						
No	9432 (96.9)	284 (94.4)	1.00 (referent)	.01	1.00 (referent)	.02
Yes	275 (2.8)	17 (5.6)	2.05 (1.23 to 3.42)		1.97 (1.17 to 3.32)	
Lifestyle						
Duration of cigarette smoking						
Nonsmoker	6460 (42.9)	200 (36.3)	1.00 (referent)	<.001	1.00 (referent)	<.001
1–19 y	2717 (18.0)	97 (17.6)	1.04 (0.81 to 1.34)		1.07 (0.83 to 1.39)	
20–29 y	1649 (10.9)	69 (12.5)	1.35 (1.00 to 1.80)		1.34 (1.00 to 1.81)	
30–39 y	1644 (10.9)	58 (10.5)	1.31 (0.96 to 1.79)		1.28 (0.93 to 1.76)	
40+ y	1570 (10.4)	71 (12.9)	1.87 (1.38 to 2.54)		1.92 (1.41 to 2.62)	
Smoker, duration unknown	100 (0.7)	10 (1.8)	4.57 (2.30 to 9.07)		4.44 (2.14 to 9.25)	
History of alcohol consumption						
Nondrinker	2715 (18.9)	115 (21.5)	1.00 (referent)	.003	1.00 (referent)	<.001
Drinker (at least 1 drink per month)	7269 (50.6)	253 (47.3)	0.67 (0.52 to 0.87)		0.64 (0.49 to 0.82)	
Recreational sun exposure (h/wk)						
Q1 (low)	2234 (20.6)	85 (21.8)	1.00 (referent)	.1	—	—
Q2	2332 (21.6)	89 (22.8)	0.97 (0.71 to 1.32)		—	—
Q3	2159 (20.0)	59 (15.1)	0.69 (0.49 to 0.98)		—	—
Q4 (high)	2983 (27.6)	98 (25.1)	0.79 (0.58 to 1.07)		—	—
Family history						
First-degree family history, any hematologic malignancy						
No	8865 (86.4)	302 (77.0)	1.00 (referent)	.003	1.00 (referent)	.002
Yes	518 (5.0)	32 (8.2)	1.86 (1.26 to 2.74)		1.92 (1.30 to 2.84)	
Occupational risk factors						
Electrical fitters						
No	7730 (98.6)	257 (94.5)	1.00 (referent)	.010	1.00 (referent)	.1
Yes	84 (1.1)	9 (3.3)	2.90 (1.42 to 5.92)		2.89 (1.41 to 5.95)	
Textile worker						
No	9177 (92.4)	298 (88.7)	1.00 (referent)	.04	1.00 (referent)	.04
Yes	744 (7.5)	30 (8.9)	1.55 (1.03 to 2.33)		1.58 (1.05 to 2.38)	
Ever lived or worked on a farm						
No	7842 (66.7)	271 (71.9)	1.00 (referent)	.02	1.00 (referent)	.02
Yes	3648 (31.0)	92 (24.4)	0.73 (0.55 to 0.95)		0.72 (0.55 to 0.95)	

*CI = confidence interval; OR = odds ratio.

risk. Indeed, atopic conditions are inversely associated with risk of B-cell lymphomas (32), but any relationship with T-cell lymphomas is not known. Our findings support an inverse association between PTCL with any allergy and a positive association between eczema and PTCL risk, consistent with previous reports among overall T-cell lymphoma (28).

Occupational groups previously linked to NHL risk include farmers, livestock workers, printers, teachers, wood workers, dry cleaners, barbers, and hairdressers (20,21). Based on our data, we observed an increase in risk of PTCL and, specifically, ALCL, for textile workers. Exposures related to textile work include: dust, endotoxin (a bacterial contaminant of raw cotton fiber and cotton dust), assorted dyes, and chemicals such as trichloroethylene,

which has previously been linked to lymphoma risk (33–38). We also report that electrical fitters had increased odds of developing ALCL and angioimmunoblastic lymphoma. Electrical workers can be dermally exposed to polychlorinated biphenyls, which have been linked to NHL risk in a number of studies (39–50), though not all. Our results warrant further investigation specifically among PTCLs. Given the large number of occupations tested, these results require replication before any conclusions can be drawn.

Lifestyle factors previously implicated in the NHL literature include smoking, which has been linked to an increase in risk of follicular lymphoma for reference (51,52), and alcohol consumption, which has been inversely associated with overall NHL (53). The current analyses showed an increased risk of PTCL with long-term

Table 3. Peripheral T-cell lymphoma-not otherwise specified (n = 234): basic analysis (adjusted for age, race, sex, and study) and final model (adjusted for age, race, sex, study, and all other variables in the model)*

	Controls, N (%)	Cases, N (%)	Basic OR (95% CI)	P	Final OR (95% CI)	P
Medical history						
Celiac disease						
No	10 501 (97.9)	159 (94.6)	1.00 (referent)	.04	1.00 (referent)	.03
Yes	26 (0.2)	2 (1.2)	7.21 (1.66 to 31.3)		8.66 (1.97 to 38.1)	
Allergy						
No	9852 (69.5)	154 (71.6)	1.00 (referent)	.04	1.00 (referent)	.03
Yes	3458 (24.4)	40 (18.6)	0.68 (0.46 to 0.99)		0.67 (0.46 to 0.98)	
Eczema						
No	13 108 (85.1)	190 (83.3)	1.00 (referent)	.7	—	—
Yes	1543 (10.0)	23 (10.1)	1.09 (0.70 to 1.72)		—	
Psoriasis						
No	9432 (96.9)	131 (94.2)	1.00 (referent)	.04	1.00 (referent)	.04
Yes	275 (2.8)	8 (5.8)	2.41 (1.16 to 5.04)		2.41 (1.15 to 5.04)	
Lifestyle						
Duration of cigarette smoking						
Nonsmoker	6460 (42.9)	82 (36.6)	1.00 (referent)	.07	1.00 (referent)	.06
1–19 y	2717 (18.0)	36 (16.1)	0.94 (0.63 to 1.42)		0.99 (0.66 to 1.49)	
20–29 y	1649 (10.9)	25 (11.2)	1.12 (0.70 to 1.79)		1.15 (0.71 to 1.84)	
30–39 y	1644 (10.9)	23 (10.3)	1.16 (0.71 to 1.90)		1.15 (0.70 to 1.88)	
40+ y	1570 (10.4)	35 (15.6)	1.75 (1.13 to 2.70)		1.76 (1.14 to 2.72)	
Smoker, duration unknown	100 (0.7)	4 (1.8)	3.36 (1.19 to 9.54)		3.61 (1.26 to 10.4)	
History of alcohol consumption						
Nondrinker	2715 (18.9)	54 (24.4)	1.00 (referent)	.02	1.00 (referent)	.01
Drinker (at least 1 drink per month)	7269 (50.6)	107 (48.4)	0.64 (0.44 to 0.92)		0.65 (0.45 to 0.93)	
Recreational sun exposure (h/wk)						
Q1 (low)	2234 (20.6)	28 (19.4)	1.00 (referent)	.3	—	—
Q2	2332 (21.6)	34 (23.6)	1.16 (0.70 to 1.93)		—	
Q3	2159 (20.0)	21 (14.6)	0.72 (0.40 to 1.29)		—	
Q4 (high)	2983 (27.6)	43 (29.9)	1.10 (0.67 to 1.79)		—	
Family history						
First-degree family history, any hematologic malignancy						
No	8865 (86.4)	120 (78.4)	1.00 (referent)	.04	1.00 (referent)	.04
Yes	518 (5.0)	13 (8.5)	1.93 (1.07 to 3.50)		1.92 (1.05 to 3.49)	
Occupational risk factors						
Electrical fitters						
No	7730 (98.6)	116 (96.7)	1.00 (referent)	.5	—	—
Yes	84 (1.1)	2 (1.3)	1.67 (0.40 to 6.96)		—	
Textile worker						
No	9177 (92.4)	131 (89.1)	1.00 (referent)	.4	—	—
Yes	744 (7.5)	14 (9.5)	1.25 (0.70 to 2.26)		—	
Ever lived or worked on a farm						
No	7842 (66.7)	117 (68.8)	1.00 (referent)	.2	—	—
Yes	3648 (31.0)	46 (27.1)	0.77 (0.52 to 1.14)		—	

*CI = confidence interval; OR = odds ratio.

smoking and a decreased risk with alcohol consumption. Although sunlight exposure is inversely associated with NHL development (54), no such associations have previously been explored specifically for T-cell lymphomas (33). The decreased risk of ALCL that we observed in association with recreational sun exposure is thus novel and requires replication.

Interestingly, our results for PTCL and PTCL subtypes appear distinct from those findings for another T-cell lymphoma subtype, mycosis fungoides or Sézary syndrome, the results for which are presented separately in this issue. Because they involve the same anatomical site, we had hypothesized that the findings would be similar for cutaneous PTCL-NOS and mycosis fungoides or Sézary syndrome, but that was not the case, providing

support for etiologic differences between these specific T-cell lymphoma subtypes, despite occurring in the same anatomic site.

The strengths of the current analyses include the large number of incident histologically confirmed PTCL cases and the broad scope of risk factors that were harmonized and evaluated, allowing the exploration of etiologic heterogeneity across PTCL subtypes. Despite the broad array of exposures evaluated, most were self-reported and, therefore, subject to recall bias. Moreover, data about specific associations with infections that are established risk factors for specific PTCL subtypes were not available. However, in the absence of direct evaluation of *H. pylori* infection, we found peptic ulcers to be associated with an increased risk of enteropathy-type PTCL.

Table 4. Anaplastic large cell lymphoma (n = 164): basic analysis (adjusted for age, race, sex, and study) and final model (adjusted for age, race, sex, study, and all other variables in the model)*

	Controls, N (%)	Cases, N (%)	Basic OR (95% CI)	P	Final OR (95% CI)	P
Medical history						
Celiac disease						
No	9363 (99.5)	105 (94.6)	1.00 (referent)	<.001	1.00 (referent)	<.001
Yes	26 (0.3)	5 (4.5)	20.92 (7.53 to 58.10)		16.59 (3.27 to 84.3)	
Allergy						
No	9852 (69.3)	103 (68.2)	1.00 (referent)	.05	—	—
Yes	3458 (24.4)	37 (24.5)	0.68 (0.45 to 1.01)		—	
Eczema						
No	12 751 (84.8)	131 (80.9)	1.00 (referent)	.5	—	—
Yes	1527 (10.2)	23 (14.1)	1.16 (0.74 to 1.84)		—	
Psoriasis						
No	9072 (96.9)	91 (91.9)	1.00 (referent)	.02	1.00 (referent)	0.2
Yes	260 (2.8)	8 (8.1)	2.63 (1.24 to 5.55)		2.73 (0.45 to 16.6)	
Lifestyle						
Duration of cigarette smoking						
Nonsmoker	6280 (42.7)	60 (37.7)	1.00 (referent)	.03	1.00 (referent)	.06
1–19 y	2649 (18.0)	35 (22.0)	1.13 (0.74 to 1.74)		1.19 (0.77 to 1.84)	
20–29 y	1601 (10.9)	19 (11.9)	1.34 (0.78 to 2.31)		1.39 (0.80 to 2.40)	
30–39 y	1597 (10.9)	16 (10.1)	1.51 (0.84 to 2.72)		1.41 (0.77 to 2.58)	
40+ y	1539 (10.5)	16 (10.1)	2.38 (1.27 to 4.48)		2.46 (1.30 to 4.65)	
Smoker, duration unknown	99 (0.7)	3 (1.9)	6.81 (1.98 to 23.44)		5.26 (1.31 to 21.1)	
History of alcohol consumption						
Nondrinker	2557 (18.3)	25 (16.6)	1.00 (referent)	.3	—	—
Drinker (at least 1 drink per month)	7057 (50.0)	67 (44.4)	0.78 (0.47 to 1.29)		—	
Recreational sun exposure (h/wk)						
Q1 (low)	2234 (20.6)	31 (24.8)	1.00 (referent)	.04	1.00 (referent)	.08
Q2	2332 (21.6)	32 (25.6)	0.76 (0.46 to 1.27)		0.80 (0.47 to 1.37)	
Q3	2159 (20.0)	17 (13.6)	0.57 (0.31 to 1.04)		0.54 (0.28 to 1.07)	
Q4 (high)	2983 (27.6)	27 (21.6)	0.49 (0.29 to 0.83)		0.48 (0.26 to 0.88)	
Family history						
First-degree family history, any hematologic malignancy						
No	8519 (86.2)	74 (79.6)	1.00 (referent)	.5	—	—
Yes	492 (5.0)	5 (5.4)	1.36 (0.54 to 3.44)		—	
Occupational risk factors						
Electrical fitters						
No	7730 (98.6)	64 (90.1)	1.00 (referent)	.02	1.00 (referent)	.03
Yes	84 (1.1)	4 (5.6)	4.45 (1.52 to 13.06)		4.08 (1.36 to 12.2)	
Textile worker						
No	9177 (92.4)	73 (86.9)	1.00 (referent)	.02	1.00 (referent)	.02
Yes	744 (7.5)	9 (10.7)	2.71 (1.27 to 5.77)		2.60 (1.21 to 5.58)	
Ever lived or worked on a farm						
No	7842 (66.7)	64 (71.1)	1.00 (referent)	.9	—	—
Yes	3648 (31.0)	24 (26.7)	0.96 (0.56 to 1.64)		—	

*CI = confidence interval; OR = odds ratio.

Another important limitation is that despite best efforts from participating studies to ascertain a representative sample of cases, PTCLs are largely aggressive and fatal, resulting in a potential survival bias among participating cases. Indeed, this was evident in the distribution of PTCL cases, whereby most were classified as nodal (PTCL-NOS, ALCL, and angioimmunoblastic), with extranodal PTCLs, the most aggressive PTCLs, largely under-represented (eg, nasal natural killer or T-cell lymphoma, enteropathy-associated PTCL, hepatosplenic PTCL, subcutaneous panniculitis-like PTCL) compared with clinical series and cancer registry data (2). It is, therefore, possible that etiologic risk factors relevant for aggressive and extranodal PTCLs were missed in this pooled analysis. The sample size was modest for stratified analyses, thereby limiting our ability to detect effect modification by

factors such as race and ethnicity and anatomic site, and we lacked information on clinically relevant markers for some subtypes, such as CD30 or ALK status for ALCL, although the etiologic importance of such clinical factors is unknown. Finally, we cannot rule out the possibility that the associations reported were due to chance, especially given the number of associations tested. Our results should therefore be used as a guide for future investigations in the epidemiology of PTCL.

In summary, in this largest epidemiologic study of PTCL cases and controls to date, we have identified a number of risk factors specific to PTCL and PTCL subtypes. Our results suggest that T-cell lymphomas and their distinct subtypes should be studied separately from other lymphoid malignancies. Future studies that pool data from cohort studies to establish

Table 5. Angioimmunoblastic lymphoma (n = 81): basic analysis (adjusted for age, race, sex, and study) and final model (adjusted for age, race, sex, study, and all other variables in the model)*

	Controls, N (%)	Cases, N (%)	Basic OR (95% CI)	P	Final OR (95% CI)	P
Medical history						
Celiac disease						
No	9363 (99.5)	62 (100)	1.00 (referent)	—	—	—
Yes	26 (0.3)	0 (0)	—	—	—	—
Allergy						
No	9597 (73.1)	57 (74.0)	1.00 (referent)	.1	—	—
Yes	3253 (24.8)	18 (23.4)	0.64 (0.35 to 1.14)		—	
Eczema						
No	12 622 (84.7)	66 (82.5)	1.00 (referent)	.1	—	—
Yes	1517 (10.2)	12 (15.0)	1.70 (0.90 to 3.20)		—	
Psoriasis						
No	9072 (96.9)	33 (100)	1.00 (referent)	—	—	—
Yes	260 (2.8)	0 (0)	—	—	—	—
Lifestyle						
Duration of cigarette smoking						
Nonsmoker	6033 (44.7)	32 (45.7)	1.00 (referent)	.2	—	—
1–19 y	2539 (18.8)	8 (11.4)	0.61 (0.27 to 1.34)		—	
20–29 y	1537 (11.4)	11 (15.7)	1.26 (0.61 to 2.60)		—	
30–39 y	1533 (11.4)	7 (10.0)	0.85 (0.37 to 1.99)		—	
40+ y	1481 (11.0)	9 (12.9)	1.32 (0.60 to 2.93)		—	
Smoker, duration unknown	97 (0.7)	2 (2.9)	5.29 (1.15 to 24.4)		—	
History of alcohol consumption						
Nondrinker	2358 (18.4)	19 (28.4)	1.00 (referent)	.1	—	—
Drinker (at least 1 drink per month)	6723 (52.5)	35 (52.2)	0.59 (0.31 to 1.13)		—	
Recreational sun exposure (h/wk)						
Q1 (low)	2136 (21.9)	11 (24.4)	1.00 (referent)	.9	—	—
Q2	2202 (22.6)	10 (22.2)	1.07 (0.44 to 2.58)		—	
Q3	2064 (21.1)	8 (17.8)	0.79 (0.31 to 2.02)		—	
Q4 (high)	2844 (29.1)	14 (31.1)	1.08 (0.47 to 2.48)		—	
Family history						
First-degree family history, any hematologic malignancy						
No	8170 (88.7)	42 (72.4)	1.00 (referent)	.05	1.00 (referent)	.05
Yes	450 (4.9)	7 (12.1)	2.55 (1.11 to 5.90)		2.55 (1.10 to 5.89)	
Occupational risk factors						
Electrical fitters						
No	7730 (98.6)	28 (93.3)	1.00 (referent)	.07	1.00 (referent)	.07
Yes	84 (1.1)	2 (6.7)	5.31 (1.18 to 23.93)		5.45 (1.20 to 24.7)	
Textile worker						
No	9177 (92.4)	41 (93.2)	1.00 (referent)	.9	—	—
Yes	744 (7.5)	3 (6.8)	1.07 (0.31 to 3.66)		—	
Ever lived or worked on a farm						
No	7842 (66.7)	39 (79.6)	1.00 (referent)	.08	—	—
Yes	3648 (31.0)	9 (18.4)	0.50 (0.22 to 1.12)		—	

*CI = confidence interval; OR = odds ratio.

the temporality of select exposures may be required. Merging of epidemiological data with large clinical series may also prove fruitful, particularly if etiologic risk factors also influence the clinical course of disease. Future studies allowing stratification by race or ethnicity and the study of rare subtypes as well as possible gene–environment associations should also be informative. Targeted studies of established risk factors such as celiac disease and identifying biological mechanisms underlying refractory celiac disease and inflammatory processes involved in T-cell lymphomas would also be particularly informative. We support the conduct of follow-up studies to confirm or refute these detected associations and to explore the possible underlying biological mechanisms.

References

1. Foss FM, Zinzani PL, Vose JM, Gascoyne RD, Rosen ST, Tobinai K. Peripheral T-cell lymphoma. *Blood*. 2011;117(25):6756–6767.
2. Wang SS, Vose J.M. Epidemiology and prognosis of T-cell lymphoma. In: Foss FM, ed. *T-Cell Lymphomas*. New York, NY: Springer; 2013:25–39.
3. 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.
4. Armitage JO. The aggressive peripheral T-cell lymphomas: 2013. *Am J Hematol*. 2013;88(10):910–918.
5. Armitage JO. Peripheral T-cell lymphomas: their time has come. *Oncology (Williston Park)*. 2009;23(13):1151–1152.
6. Federico M, Rudiger T, Bellei M, et al. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. *J Clin Oncol*. 2013;31(2):240–246.

7. Iqbal J, Weisenburger DD, Greiner TC, et al.; International Peripheral T-Cell Lymphoma Project. Molecular signatures to improve diagnosis in peripheral T-cell lymphoma and prognostication in angioimmunoblastic T-cell lymphoma. *Blood*. 2010;115(5):1026–1036.
8. Mitrovic Z, Perry AM, Suzumiya J, et al. The prognostic significance of lymphopenia in peripheral T-cell and natural killer/T-cell lymphomas: a study of 826 cases from the International Peripheral T-cell Lymphoma Project. *Am J Hematol*. 2012;87(8):790–794.
9. Savage KJ, Harris NL, Vose JM, et al.; International Peripheral T-Cell Lymphoma Project. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2008;111(12):5496–5504.
10. Vose J, Armitage J, Weisenburger D; International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;26(25):4124–4130.
11. Weisenburger DD, Savage KJ, Harris NL, et al.; International Peripheral T-cell Lymphoma Project. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. *Blood*. 2011;117(12):3402–3408.
12. Shapira MY, Caspi O, Amir G, Zlotogorski A, Naparstek Y. Gastric-mucocutaneous gammadelta T cell lymphoma: possible association with Epstein-Barr virus? *Leuk Lymphoma*. 1999;35(3-4):397–401.
13. Thompson PA, Prince HM. Breast implant-associated anaplastic large cell lymphoma: a systematic review of the literature and mini-meta analysis. *Curr Hematol Malig Rep*. 2013;8(3):196–210.
14. Lista F, Tutino R, Khan A, Ahmad J. Subglandular breast augmentation with textured, anatomic, cohesive silicone implants: a review of 440 consecutive patients. *Plast Reconstr Surg*. 2013;132(2):295–303.
15. Taylor CR, Siddiqi IN, Brody GS. Anaplastic large cell lymphoma occurring in association with breast implants: review of pathologic and immunohistochemical features in 103 cases. *Appl Immunohistochem Mol Morphol*. 2013;21(1):13–20.
16. Jewell M, Spear SL, Largent J, Oefelein MG, Adams WP Jr. Anaplastic large T-cell lymphoma and breast implants: a review of the literature. *Plast Reconstr Surg*. 2011;128(3):651–661.
17. Kim B, Roth C, Chung KC, et al. Anaplastic large cell lymphoma and breast implants: a systematic review. *Plast Reconstr Surg*. 2011;127(6):2141–2150.
18. de Jong D, Vasmel WL, de Boer JP, et al. Anaplastic large-cell lymphoma in women with breast implants. *JAMA*. 2008;300(17):2030–2035.
19. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2001.
20. 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.
21. 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.
22. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
23. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–1558.
24. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
25. Horton NJ, Kleinman KP. Much ado about nothing: a comparison of missing data methods and software to fit incomplete data regression models. *Am Stat*. 2007;61(1):79–90.
26. Yucel RM. State of the multiple imputation software. *J Stat Softw*. 2011;45(1):1–7.
27. 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.
28. Ekström Smedby K, Vajdic CM, Falster M, et al. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood*. 2008;111(8):4029–4038.
29. Catassi C, Bearzi I, Holmes GK. Association of celiac disease and intestinal lymphomas and other cancers. *Gastroenterology*. 2005;128(4 suppl 1):S79–S86.
30. Bagdi E, Diss TC, Munson P, Isaacson PG. Mucosal intra-epithelial lymphocytes in enteropathy-associated T-cell lymphoma, ulcerative jejunitis, and refractory celiac disease constitute a neoplastic population. *Blood*. 1999;94(1):260–264.
31. Mention JJ, Ben Ahmed M, Bègue B, et al. Interleukin 15: a key to disrupted intraepithelial lymphocyte homeostasis and lymphomagenesis in celiac disease. *Gastroenterology*. 2003;125(3):730–745.
32. 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.
33. Chiu WA, Jinot J, Scott CS, et al. Human health effects of trichloroethylene: key findings and scientific issues. *Environ Health Perspect*. 2013;121(3):303–311.
34. Cocco P, Vermeulen R, Flore V, et al. Occupational exposure to trichloroethylene and risk of non-Hodgkin lymphoma and its major subtypes: a pooled InterLymph [correction of InterLymph] analysis. *Occup Environ Med*. 2013;70(11):795–802.
35. Karami S, Bassig B, Stewart PA, et al. Occupational trichloroethylene exposure and risk of lymphatic and haematopoietic cancers: a meta-analysis. *Occup Environ Med*. 2013;70(8):591–599.
36. Mandel JH, Kelsh M, Mink PJ, Alexander DD. Trichloroethylene exposure and non-Hodgkin's lymphoma: supportive evidence. *Occup Environ Med*. 2008;65(2):147–148.
37. Mandel JH, Kelsh MA, Mink PJ, et al. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: a meta-analysis and review. *Occup Environ Med*. 2006;63(9):597–607.
38. Purdue MP, Bakke B, Stewart P, et al. A case-control study of occupational exposure to trichloroethylene and non-Hodgkin lymphoma. *Environ Health Perspect*. 2011;119(2):232–238.
39. Bertrand KA, Spiegelman D, Aster JC, et al. Plasma organochlorine levels and risk of non-Hodgkin lymphoma in a cohort of men. *Epidemiology*. 2010;21(2):172–180.
40. Cocco P, Brennan P, Ibba A, et al. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. *Occup Environ Med*. 2008;65(2):132–140.
41. De Roos AJ, Hartge P, Lubin JH, et al. Persistent organochlorine chemicals in plasma and risk of non-Hodgkin's lymphoma. *Cancer Res*. 2005;65(23):11214–11226.
42. Engel LS, Laden F, Andersen A, et al. Polychlorinated biphenyl levels in peripheral blood and non-Hodgkin's lymphoma: a report from three cohorts. *Cancer Res*. 2007;67(11):5545–5552.
43. Engel LS, Lan Q, Rothman N. Polychlorinated biphenyls and non-Hodgkin lymphoma. *Cancer Epidemiol Biomarkers Prev*. 2007;16(3):373–376.
44. Freeman MD, Kohles SS. Plasma levels of polychlorinated biphenyls, non-Hodgkin lymphoma, and causation. *J Environ Public Health*. 2012;2012:258981.
45. Hardell K, Carlberg M, Hardell L, et al. Concentrations of organohalogen compounds and titres of antibodies to Epstein-Barr virus antigens and the risk for non-Hodgkin lymphoma. *Oncol Rep*. 2009;21(6):1567–1576.
46. Kramer S, Hikel SM, Adams K, Hinds D, Moon K. Current status of the epidemiologic evidence linking polychlorinated biphenyls and non-Hodgkin lymphoma, and the role of immune dysregulation. *Environ Health Perspect*. 2012;120(8):1067–1075.
47. Laden F, Bertrand KA, Altshul L, Aster JC, Korrick SA, Sagiv SK. Plasma organochlorine levels and risk of non-Hodgkin lymphoma in the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19(5):1381–1384.
48. Maifredi G, Donato F, Magoni M, et al. Polychlorinated biphenyls and non-Hodgkin's lymphoma: a case-control study in Northern Italy. *Environ Res*. 2011;111(2):254–259.

49. Rothman N, Cantor KP, Blair A, et al. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. *Lancet*. 1997;350(9073):240–244.
50. Spinelli JJ, Ng CH, Weber JP, et al. Organochlorines and risk of non-Hodgkin lymphoma. *Int J Cancer*. 2007;121(12):2767–2775.
51. Gibson TM, Smedby KE, Skibola CF, et al. Smoking, variation in N-acetyltransferase 1 (NAT1) and 2 (NAT2), and risk of non-Hodgkin lymphoma: a pooled analysis within the InterLymph consortium. *Cancer Causes Control*. 2013;24(1):125–134.
52. 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):925–933.
53. Morton LM, Zheng T, Holford TR, et al.; InterLymph Consortium. Alcohol consumption and risk of non-Hodgkin lymphoma: a pooled analysis. *Lancet Oncol*. 2005;6(7):469–476.
54. Krickler A, Armstrong BK, Hughes AM, et al.; Interlymph Consortium. Personal sun exposure and risk of non Hodgkin lymphoma: a pooled analysis from the Interlymph Consortium. *Int J Cancer*. 2008;122(1):144–154.

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Supplemental Table 1. ALCL, by age (basic analysis only)

	<30 years							30+ years						
	Controls		Cases		OR (95% CI)		P	Controls		Cases		OR (95% CI)		P
	No.	(%)	No.	(%)				No.	(%)	No.	(%)			
Medical history														
Hay fever														
No	503	(64.7)	21	(77.8)	1.00 (referent)		0.018	9223	(65.7)	76	(59.8)	1.00 (referent)		0.634
Yes	167	(21.5)	2	(7.4)	0.23 (0.05 - 1.00)			2673	(19.0)	28	(22.0)	0.89 (0.55 - 1.44)		
Eczema														
No	647	(80.5)	23	(71.9)	1.00 (referent)		0.198	12041	(85.0)	108	(83.1)	1.00 (referent)		0.894
Yes	134	(16.7)	8	(25.0)	1.83 (0.75 - 4.42)			1386	(9.8)	15	(11.5)	1.04 (0.60 - 1.81)		
Celiac disease														
No	203	(98.5)	3	(100.0)	1.00 (referent)		0.813	8730	(99.5)	82	(93.2)	1.00 (referent)		<0.001
Yes	2	(1.0)	0	(0.0)	-	-		24	(0.3)	5	(5.7)	25.18 (8.93 - 71.0)		
Psoriasis														
No	352	(97.0)	16	(100.0)	1.00 (referent)		0.334	8422	(96.8)	70	(89.7)	1.00 (referent)		0.009
Yes	10	(2.8)	0	(0.0)	-	-		248	(2.9)	8	(10.3)	3.19 (1.50 - 6.80)		
History of autoimmune disease														
No autoimmune disease	722	(96.9)	26	(100.0)	1.00 (referent)		0.595	13957	(95.4)	115	(87.8)	1.00 (referent)		0.008
B-cell activation	4	(0.5)	0	(0.0)	-	-		130	(0.9)	2	(1.5)	2.23 (0.53 - 9.33)		
T-cell activation	18	(2.4)	0	(0.0)	-	-		531	(3.6)	14	(10.7)	3.03 (1.70 - 5.39)		
Both	1	(0.1)	0	(0.0)	-	-		12	(0.1)	0	(0.0)	-	-	
Lifestyle														
Duration of cigarette smoking														
Non-smoker	444	(56.0)	14	(43.8)	1.00 (referent)		0.154	5813	(42.0)	46	(36.2)	1.00 (referent)		0.083
1-19 years	319	(40.2)	16	(50.0)	1.86 (0.86 - 4.04)			2289	(16.6)	19	(15.0)	0.91 (0.53 - 1.56)		
20-29 years	2	(0.3)	0	(0.0)	-	-		1599	(11.6)	19	(15.0)	1.22 (0.70 - 2.11)		
30-39 years	-	-	-	-	-	-		1597	(11.5)	16	(12.6)	1.38 (0.77 - 2.50)		
40+ years	-	-	-	-	-	-		1539	(11.1)	16	(12.6)	2.19 (1.16 - 4.13)		
Smoker, duration unknown	4	(0.5)	1	(3.1)	-	(1.33 -∞)		95	(0.7)	2	(1.6)	5.67 (1.30 - 24.8)		
Recreational sun exposure (hrs/week)														
Q1 (low)	89	(14.7)	2	(9.1)	1.00 (referent)		0.717	2142	(21.1)	29	(28.2)	1.00 (referent)		0.023
Q2	160	(26.4)	8	(36.4)	1.61 (0.31 - 8.38)			2166	(21.3)	24	(23.3)	0.69 (0.40 - 1.21)		
Q3	122	(20.1)	4	(18.2)	2.09 (0.33 -13.41)			2033	(20.0)	13	(12.6)	0.47 (0.24 - 0.91)		
Q4 (high)	206	(34.0)	7	(31.8)	1.03 (0.20 - 5.45)			2770	(27.3)	20	(19.4)	0.44 (0.24 - 0.78)		
Occupational risk factors														
Textile worker														
No	395	(95.0)	7	(77.8)	1.00 (referent)		0.03	8609	(92.1)	61	(87.1)	1.00 (referent)		0.095

Yes	12	(2.9)	2	(22.2)	10.5	(1.65 - 67.4)	732	(7.8)	7	(10.0)	2.17	(0.94 - 5.02)	
Electrical fitters													
No	397	(95.4)	9	(100.0)	1.00	(referent)	0.415	7237	(98.8)	53	(89.8)	1.00 (referent)	0.007
Yes	10	(2.4)	0	(0.0)	-	-		74	(1.0)	4	(6.8)	6.30	(2.11 - 18.8)

Supplemental Table 2. Primary cutaneous ALCL (n=45): basic (adjusted for age, race, sex, study) and final model (adjusted for age, race, sex, study and all other variables in model)

	Controls No. (%)		Cases No. (%)		Basic OR (95% CI)		P	Final OR (95% CI)		P
Medical history										
Hay fever										
No	7410	(74.3)	11	(28.2)	1.00 (referent)		0.001	1.00 (referent)		0.001
Yes	2098	(21.0)	18	(46.2)	3.94 (1.72 - 9.03)			6.38 (1.77 – 23.0)		
Celiac disease										
No	8671	(99.4)	27	(87.1)	1.00 (referent)		0.026	1.00 (referent)		0.03
Yes	24	(0.3)	1	(3.2)	∞ (3.96 - ∞)			39.91 (3.15 - 506.4)		
Lifestyle										
Duration of cigarette smoking										
Non-smoker	5262	(44.9)	8	(23.5)	1.00 (referent)		0.041	1.00 (referent)		0.046
1-19 years	2225	(19.0)	8	(23.5)	2.06 (0.74 - 5.78)			2.08 (0.73 - 5.90)		
20-29 years	1318	(11.2)	6	(17.6)	3.70 (1.19 - 11.52)			3.62 (1.13 - 11.55)		
30-39 years	1325	(11.3)	4	(11.8)	2.97 (0.80 - 10.96)			3.20 (0.86 - 11.93)		
40+ years	1228	(10.5)	6	(17.6)	5.46 (1.60 - 18.66)			5.82 (1.63 - 20.80)		
Smoker, duration unknown	87	(0.7)	1	(2.9)	∞ (1.83 - ∞)			16.37 (1.46 - 183.4)		

Supplemental Table 3. PTCL – Cutaneous NOS (n=27): basic (adjusted for age, race, sex, study) and final model (adjusted for age, race, sex, study and all other variables in model)

	Controls No. (%)		Cases No. (%)		Basic OR (95% CI)*		P	Final OR (95% CI)		P
Medical history										
Asthma and other atopic conditions†										
None	5388	(82.1)	12	(48.0)	1.00 (referent)		0.003	1.00 (referent)		0.002
Asthma only	218	(3.3)	0	(0.0)	-	-		-		
Asthma with allergy, hay fever, and/or eczema	353	(5.4)	5	(20.0)	9.47	(2.74 - 32.7)		10.2	(2.90 - 35.5)	
Occupational risk factors										
Fire Fighter										
No	5325	(99.1)	20	(90.9)	1.00 (referent)		0.016	1.00 (referent)		0.013
Yes	36	(0.7)	2	(9.1)	12.4	(2.42 - 63.3)		15.2	(2.69 - 85.7)	

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

Supplemental Table 4. PTCL enteropathy-type lymphoma (n=23): basic (adjusted for age, race, sex, study) and final model (adjusted for age, race, sex, study and all other variables in model)

	Controls No. (%)		Cases No. (%)		Basic OR (95% CI)*		P	Final OR (95% CI)		P
Medical history										
Celiac disease										
No	6068	(99.4)	6	(60.0)	1.00	(referent)	<0.001	1.00 (referent)	<0.001	
Yes	18	(0.3)	4	(40.0)	309.56	(67.03-1429.5)		215.1 (44.7-1041.2)		
Number of years from 1st transfusion to date of diagnosis										
No transfusion	5075	(79.9)	13	(81.3)	1.00	(referent)	0.161	1.00 (referent)	0.096	
≤20 years	454	(7.1)	1	(6.3)	1.09	(0.14 - 8.49)		1.05 (0.12-9.17)		
20-39 years	360	(5.7)	0	(0.0)	-	-		-		
40+ years	156	(2.5)	2	(12.5)	6.65	(1.32 - 33.57)		9.33 (1.74-50.11)		
Peptic Ulcer										
No	4037	(93.3)	10	(66.7)	1.00	(referent)	<0.001	1.00 (referent)	0.002	
Yes	261	(6.0)	5	(33.3)	9.64	(3.11 - 29.88)		8.69 (2.54-29.78)		
Occupational risk factors										
Textile worker										
No	4663	(92.6)	11	(78.6)	1.00	(referent)	0.04	1.00 (referent)	0.054	
Yes	360	(7.1)	3	(21.4)	5.08	(1.32 - 19.59)		5.06 (1.16-22.02)		

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