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

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Background Little is known about the etiology of hairy cell leukemia (HCL), a rare B-cell lymphoproliferative disorder with marked male predominance. Our aim was to identify key risk factors for HCL.

Methods A pooled analysis of individual-level data for 154 histologically confirmed HCL cases and 8834 controls from five case–control studies, conducted in Europe and Australia, was undertaken. Age-, race and/or ethnicity-, sex-, and study-adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using unconditional logistic regression.

Results The usual patterns for age and sex in HCL were observed, with a median age of 55 years and sex ratio of 3.7 males to females. Cigarette smoking was inversely associated with HCL (OR = 0.51, 95% CI = 0.37 to 0.71) with dose–response relationships observed for duration, frequency, and lifetime cigarette smoking (P_{trend} < .001). In contrast, occupation as a farmer was positively associated with HCL (OR = 2.34, 95% CI = 1.36 to 4.01), with a dose–response relationship observed for duration (OR = 1.82, 95% CI = 0.85 to 3.88 for ≤10 years vs never; and OR = 2.98, 95% CI = 1.50 to 5.93 for >10 years vs never; P_{trend} = .025). Adult height was also positively associated with HCL (OR = 2.69, 95% CI = 1.39 to 5.29 for upper vs lower quartile of height). The observed associations remained consistent in multivariate analysis.

Conclusions Our observations of an increased risk of HCL from farming exposures and decreased risk from smoking exposures, independent of one another, support a multifactorial origin and an etiological specificity of HCL compared with other non-Hodgkin lymphoma subtypes. The positive association with height is a novel finding that needs replication.

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Recent data support both etiologic commonality and heterogeneity among lymphoma subtypes. Initially described by Ewald (1) in 1923 as leukemic reticuloendotheliosis, followed by the classic description of 26 cases in 1958 by Bouroncle et al. (2), hairy cell leukemia (HCL) is an indolent malignancy of mature B lymphocytes with cytoplasmic "hairy" projections, involving the peripheral blood and diffusely infiltrating the bone marrow and splenic red pulp (3). HCL is a rare subtype of non-Hodgkin lymphoma (NHL) with an estimated annual incidence of less than 1.0 per 100 000 person-years in both sexes and a clear male predominance (4–8). In contrast to the well-defined clinicopathological features of HCL, its etiology remains largely unknown, in part, because its low incidence limits the sample size required for adequate statistical power. Several putative risk factors for HCL, such as tobacco smoking and farming occupation, identified in six case–control studies published before 2000 and conducted in the United States (9,10), United Kingdom (11), France (12), Sweden (13,14) and in subgroup analyses from larger case–control studies of NHL (15–18), need confirmation. These studies assessed only a limited range of exposures for HCL and, to date, there has been only one multivariate assessment across these factors simultaneously (19).

To advance our understanding of the etiology of HCL, associations with lifestyle, medical history of atopic and autoimmune conditions, and occupational factors were investigated in an analysis of 154 cases and 8834 controls from five case–control studies from Europe (16,20–22) and Australia (23), as part of the International Lymphoma Epidemiology Consortium (InterLymph) NHL Subtypes Project (L. M. Morton et al., unpublished data).

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 HCL; and 2) availability of individual-level data for at least several factors of interest by December 31, 2011. All of the studies excluded

individuals with a known history of solid organ transplantation and/or HIV or AIDS. Contributing studies were approved by local ethics review committees, and all participants provided informed consent before interview.

NHL Subtype Classification

Using guidelines from the InterLymph Pathology Working Group (24), cases were classified according to the World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues (3,25). All five studies included in this pooled analysis had some form of centralized pathology review by at least one expert hematopathologist to confirm the diagnoses.

Risk Factor Definitions

Each study collected data on putative NHL risk factors in a standardized, structured format by in-person or telephone interviews and/or self-administered questionnaires. Factors selected for inclusion in these analyses were the available lifestyle factors, medical history of atopic and autoimmune conditions, and occupations with data from at least four individual studies in the overall InterLymph NHL Subtypes Project. Centralized harmonization of individual-level, deidentified data from each study was a key element of this pooled analysis. Each exposure variable was harmonized individually and then data were reviewed for consistency among related exposure variables. Socioeconomic status (SES) was measured by years of education for the North American studies and by dividing measures of education or SES into tertiles for studies conducted in Europe or Australia. Details of the data harmonization rules are provided elsewhere in this issue.

Statistical Analysis

Risk of HCL was examined for each exposure variable using unconditional logistic regression models adjusted for age, race and/or ethnicity, sex, and study ("basic model"). The statistical significance of each relationship 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 influential factors. Individuals with missing data for the exposure variable of interest were excluded from that analysis. To evaluate effect heterogeneity among the five studies, we performed a separate unconditional logistic regression within each study and then quantified the variability of the coefficients using the *H* statistic, adapting the definition by Higgins and Thompson (26) to categorical variables.

We then examined the relationships 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 repeated the above logistic regression analyses, stratifying individuals by age (ie, <30, 30–39, 40–49, 50–59, 60–69, 70–79, 80+), sex, race and/or ethnicity, region (ie, Southern Europe vs Northern Europe vs Australia), study site, study design (ie, population-based vs hospital- or clinic-based), and other putative risk factors identified in the analyses. Forest plots of the results from the stratified analyses were used to identify possible modifiers of the effect of an exposure variable of interest. To account for other potential confounders, we conducted three analyses. First, we evaluated the risk estimate for each putative risk factor in a series of models that adjusted for one other putative risk factor individually, together with age, race and/or ethnicity, sex, and study. Secondly, we conducted a single unconditional 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 analyses (ie, no individual dropped due to missing data). Finally, we conducted a forward stepwise unconditional logistic regression with all putative risk factors (only one factor by type of exposure that would result in the most parsimonious model), adjusting for age, sex, race and/or ethnicity, study, SES with an alpha level of 0.05 ("final model"), including factors with a two-sided *P* value less than .05.

Because the controls for most of original studies were chosen to frequency match the age and sex of all NHL cases, rather than just HCL cases, we conducted sensitivity analyses using a subset of controls frequency matched by age and sex to HCL cases. The results of 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. Analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

Results

The pooled dataset included 154 HCL cases and 8834 controls from five case–control studies (Table 1). As expected, given that the contributing studies were designed to frequency match the controls by sex and age to all NHL cases, HCL cases were more likely to be male (78.6% vs 54.8%) and tended to be younger (median age 55 vs 59) and to have a higher SES (or to be more highly educated) (43.5% vs 26.3% in the high SES category) compared with controls (ie, odds ratio [OR] = 1.60, 95% confidence interval [CI] = 1.08 to 2.41 for high vs low SES).

Basic Models

Lifestyle Factors and Anthropometric Measures. The associations between lifestyle factors, anthropometric measures, and HCL, adjusted for age, sex, race and/or ethnicity, and study ("basic model"), are presented in Table 2. Cigarette smoking defined as having "smoked longer than six months" or "more than 100 cigarettes in a lifetime," was inversely associated with HCL (OR = 0.51, 95% CI = 0.37 to 0.71). This association was statistically significant among males (OR = 0.45, 95% CI = 0.31 to 0.65), but not females (OR = 0.80, 95% CI = 0.39 to 1.37). The risk estimates were lower for current smokers (OR = 0.34, 95% CI = 0.21 to 0.55) than former smokers (OR = 0.71, 95% CI = 0.48 to 1.05), reaching statistical significance only among males. The ORs also decreased with increasing duration (years), frequency (cigarettes per day), and lifetime cigarette smoking (pack-years), with clear significant downward trends restricted to males for all three quantitative measures (*P* value for linear trend in ORs <0.001). For men, lifetime smoking more than 35 pack-years was associated with a 76% decreased risk (OR = 0.24, 95% CI = 0.11 to 0.51), whereas smoking less than or equal to 10 pack-years was associated with a 32% decreased risk.

We found no relationship between various measures of alcohol consumption and risk of HCL (Table 2). While body mass index was not associated with HCL, usual adult height tended to be higher in cases than in controls, with a statistically significant

Table 1. Descriptive characteristics of hairy cell leukemia cases and controls

	Controls, N (%)	Cases, N (%)
Total	8834 (98.3)	154 (1.7)
Study		
Europe		
Engela	722 (8.2)	36 (23.4)
EpiLymph	2460 (27.8)	15 (9.7)
Italy multicenter	1771 (20.0)	30 (19.5)
SCALE	3187 (36.1)	63 (40.9)
Australia		
New South Wales	694 (7.9)	10 (6.5)
Region		
North America	0 (0.0)	0 (0.0)
Northern Europe	5403 (61.2)	112 (72.7)
Southern Europe	2737 (31.0)	32 (20.8)
Australia	694 (7.9)	10 (6.5)
Design		
Population-based	6698 (75.8)	109 (70.8)
Hospital-based	2136 (24.2)	45 (29.2)
Age		
<30	640 (7.2)	1 (0.6)
30–39	750 (8.5)	14 (9.1)
40–49	1241 (14.0)	38 (24.7)
50–59	2072 (23.5)	48 (31.2)
60–69	2614 (29.6)	43 (27.9)
70–79	1454 (16.5)	10 (6.5)
≥80	63 (0.7)	0 (0.0)
Sex		
Male	4840 (54.8)	121 (78.6)
Female	3994 (45.2)	33 (21.4)
Race		
White, non-Hispanic	8501 (96.2)	148 (96.1)
Black	2 (0.0)	0 (0.0)
Asian	14 (0.2)	0 (0.0)
Hispanic	0 (0.0)	0 (0.0)
Other or unknown or missing	317 (3.6)	6 (3.9)
Socioeconomic status		
Low	3446 (39.0)	47 (30.5)
Medium	3015 (34.1)	39 (25.3)
High	2320 (26.3)	67 (43.5)
Other or missing	53 (0.6)	1 (0.6)
Non-Hodgkin lymphoma classification		
World Health Organization	7063 (80.0)	124 (80.5)
Working Formulation	1771 (20.0)	30 (19.5)

relationship (OR = 2.69, 95% CI = 1.39 to 5.2 for the upper vs lower sex-specific quartile of height) (Table 2).

Atopic and Autoimmune Conditions. Overall, we observed no relationship between atopic or autoimmune conditions and HCL risk (Table 3). However, there was a significant positive association between asthma and HCL risk in females (OR = 3.31, 95% CI = 1.37 to 8.03) although based on seven cases (data not shown).

Farming. Having ever lived or worked on a farm was positively associated with HCL risk (OR = 1.68, 95% CI = 1.04 to 2.71) (Table 4). Risk estimates were comparable in men and women.

Employment as a farmer was also positively associated with HCL (OR = 1.55, 95% CI = 0.95 to 2.53), significantly for having ever worked as a mixed animal and crop farmer (OR = 2.34, 95% CI = 1.36 to 4.01). A positive trend was also observed with increasing duration of occupation as a farmer (Table 4), significant for employment as a mixed animal and crop farmer (OR = 1.82, 95% CI = 0.85 to 3.88 for 1–10 years and OR = 2.98, 95% CI = 1.50 to 5.93 for >10 years; P_{trend} = .025). Increased risks between farming exposures and HCL had the same magnitude in smokers and nonsmokers (data not shown).

Sex-Specific Findings. Due to the male predominance in HCL, the number of women was small (n = 33); however, the risk estimates observed for cigarette smoking, farming occupation exposures, and height were in the same direction and of comparable magnitude as those for males, suggesting no sex specificity (Table 5). None of the *P* values for heterogeneity among sexes was statistically significant.

Final Model

In the multivariate stepwise regression analysis adjusted for age, sex, race and/or ethnicity, study, and SES (Table 6), living or working in a farm (ever vs. never), and height (as a continuous variable) were independently and positively associated with HCL risk. Cumulative cigarette exposure (in pack-years) was independently and inversely associated with HCL risk.

Secondary Analyses

No significant interstudy heterogeneity was observed for any of the following exposures: cigarette smoking, living or working on a farm, SES, or height. Furthermore, no effect modification was detected in our main results by sex, age category, region, race and/or ethnicity, study, study design (population-based vs hospital- or clinic-based), or histological classification (World Health Organization vs Working Formulation). Additional adjustments for alcohol consumption, body mass index, and history of allergy did not materially change the results.

Discussion

Our pooled analysis of 154 HCL cases and 8834 controls from five independent case–control studies showed an inverse association between cigarette smoking and HCL risk, including a significant trend with increasing lifetime cigarette consumption. We also found a positive association between farming and HCL risk, and a dose–response relationship with increasing duration of occupation as a farmer, although based on a small number of cases. The HCL cases tended to be taller than the controls. The associations for pack-years of smoking, ever lived or worked in a farm, and usual height remained unchanged when included in the same model, supporting their independent role in the etiology of HCL.

Unfortunately, the small number of cases in our study did not allow for an investigation of associations between either personal history of autoimmune disease (27) or family history of cancer (28,29) and HCL.

Despite the large number of studies published on etiological risk factors for NHL, few are specifically dedicated to HCL (9–12). Our findings on cigarette smoking and HCL corroborate the results of studies published before 2000 in the United States (9), France (12), the United Kingdom (11), and Sweden (30) (none of which is included in the present pooled analysis) and a French study published in 2008 (16) (that is included in the present analysis). However, our pooled analysis is the first to report significant

Table 2. Lifestyle factors and anthropometric measures and risk of hairy cell leukemia ("basic model")*

	Controls, N (%)	Cases, N (%)	OR (95% CI)†	*P*
History of cigarette smoking§				
No	3998 (45.3)	83 (53.9)	1.00 (referent)	<.001
Yes	4822 (54.6)	71 (46.1)	0.51 (0.37 to 0.71)	
Smoking status as of ~1 y before diagnosis or interview§				
Nonsmoker	3998 (45.3)	83 (53.9)	1.00 (referent)	<.001
Former smoker	2262 (25.6)	44 (28.6)	0.71 (0.48 to 1.05)	
Current smoker	2112 (23.9)	21 (13.6)	0.34 (0.21 to 0.55)	
Age started smoking cigarettes regularly§				
Nonsmoker	3998 (45.3)	83 (53.9)	1.00 (referent)	.003
<14 y	467 (5.3)	7 (4.5)	0.51 (0.23 to 1.11)	
14–17 y	1883 (21.3)	28 (18.2)	0.46 (0.30 to 0.72)	
18–19 y	830 (9.4)	11 (7.1)	0.48 (0.25 to 0.91)	
20+ y	1185 (13.4)	19 (12.3)	0.67 (0.40 to 1.12)	
Frequency of cigarette smoking§				
Nonsmoker	3998 (45.3)	83 (53.9)	1.00 (referent)	<.001
Smoker, 1–10 cigarettes per d	1795 (20.3)	29 (18.8)	0.65 (0.42 to 1.00)	
Smoker, 11–20 cigarettes per d	2049 (23.2)	32 (20.8)	0.49 (0.32 to 0.75)	
Smoker, 21–30 cigarettes per d	444 (5.0)	5 (3.2)	0.34 (0.13 to 0.85)	
Smoker, >30 cigarettes per d	386 (4.4)	3 (1.9)	0.22 (0.07 to 0.71)	
Duration of cigarette smoking§				
Nonsmoker	3998 (45.3)	83 (53.9)	1.00 (referent)	<.001
1–20 y	1643 (18.6)	29 (18.8)	0.69 (0.44 to 1.07)	
21–30 y	1032 (11.7)	14 (9.1)	0.39 (0.22 to 0.69)	
30–39 y	1033 (11.7)	15 (9.7)	0.44 (0.25 to 0.78)	
40+ y	1058 (12.0)	13 (8.4)	0.49 (0.27 to 0.91)	
Years since quit cigarette smoking§				
Nonsmoker	3998 (45.3)	83 (53.9)	1.00 (referent)	<.001
Former smoker, quit >25 y ago	618 (7.0)	9 (5.8)	0.61 (0.30 to 1.25)	
Former smoker, quit 16–25 y ago	605 (6.8)	11 (7.1)	0.59 (0.31 to 1.14)	
Former smoker, quit 6–15 y ago	635 (7.2)	15 (9.7)	0.87 (0.49 to 1.55)	
Former smoker, quit ≤5 y ago	368 (4.2)	7 (4.5)	0.67 (0.30 to 1.48)	
Lifetime cigarette exposure§				
Nonsmoker	3998 (45.3)	83 (53.9)	1.00 (referent)	<.001
1–10 pack-years	1502 (17.0)	25 (16.2)	0.71 (0.45 to 1.12)	
11–20 pack-years	1054 (11.9)	19 (12.3)	0.56 (0.34 to 0.94)	
21–35 pack-years	1104 (12.5)	16 (10.4)	0.44 (0.26 to 0.77)	
>35 pack-years	1001 (11.3)	9 (5.8)	0.28 (0.14 to 0.56)	
Lifetime cigarette exposure				
Continuous	8834 (100.0)	154 (100.0)	0.98 (0.96 to 0.99)	<.001
History of alcohol consumption§,‖				
Nondrinker	1395 (17.1)	14 (9.7)	1.00 (referent)	.979
Drinker (at least one drink per month)	3293 (40.5)	75 (52.1)	0.99 (0.53 to 1.84)	
Alcohol consumption status as of ~2 y before diagnosis or interview§,‖				
Nondrinker	1395 (17.1)	14 (9.7)	1.00 (referent)	.454
Former	185 (2.3)	2 (1.4)	1.02 (0.20 to 5.26)	
Current	1772 (21.8)	51 (35.4)	1.57 (0.64 to 3.89)	
Servings of alcohol per week as an adult§,‖				
Nondrinker	1395 (17.1)	14 (9.7)	1.00 (referent)	.542
<1 drink per wk	168 (2.1)	6 (4.2)	1.77 (0.65 to 4.86)	
1–6 drinks per wk	833 (10.2)	20 (13.9)	1.21 (0.58 to 2.50)	
7–13 drinks per wk	699 (8.6)	12 (8.3)	0.85 (0.38 to 1.92)	
14–27 drinks per wk	805 (9.9)	14 (9.7)	0.68 (0.31 to 1.50)	
28+ drinks/wk or binge drinkers	758 (9.3)	23 (16.0)	1.06 (0.51 to 2.20)	
Usual adult BMI (kg/m^2)§				
15–<18.5	102 (1.6)	0 (0.0)		
18.5–<22.5	1181 (18.5)	23 (20.2)	1.00 (referent)	.188
22.5–<25	1585 (24.9)	32 (28.1)	0.74 (0.42 to 1.28)	
25–<30	2374 (37.3)	43 (37.7)	0.61 (0.36 to 1.04)	

(Table continues)

Table 2 (Continued).

	Controls, N (%)	Cases, N (%)	OR (95% CI)†	P
30–<35	698 (11.0)	11 (9.6)	0.59 (0.28 to 1.26)	
35–50	210 (3.3)	1 (0.9)	0.24 (0.03 to 1.77)	
Usual adult height§				
Quartile 1 (low)	1573 (24.7)	14 (12.3)	1.00 (referent)	.009
Quartile 2	1606 (25.2)	28 (24.6)	1.62 (0.84 to 3.14)	
Quartile 3	1376 (21.6)	31 (27.2)	2.44 (1.26 to 4.73)	
Quartile 4 (high)	1595 (25.0)	37 (32.5)	2.69 (1.39 to 5.20)	
Usual adult weight§				
Quartile 1 (low)	1506 (23.6)	24 (21.1)	1.00 (referent)	.992
Quartile 2	1275 (20.0)	25 (21.9)	1.08 (0.61 to 1.91)	
Quartile 3	1786 (28.0)	33 (28.9)	1.02 (0.59 to 1.74)	
Quartile 4 (high)	1583 (24.9)	28 (24.6)	0.99 (0.57 to 1.74)	

* BMI = body mass index; CI = confidence interval; OR = odds ratio.

† OR (95% CI) adjusted for age, sex, race and/or ethnicity, and study.

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

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

|| Several centers from Scandinavian Lymphoma Etiology Study (SCALE) and Epilymph studies did not collect any information on alcohol consumption.

Table 3. Atopic and autoimmune conditions and risk of hairy cell leukemia ("basic model")*

	Controls, N (%)	Cases, N (%)	OR (95% CI)†	P
Any atopic disorder‡,§				
No	5515 (62.4)	98 (63.6)	1.00 (referent)	.925
Yes	3286 (37.2)	56 (36.4)	1.02 (0.72 to 1.44)	
Allergy§,||				
No	6614 (74.9)	115 (74.7)	1.00 (referent)	.579
Yes	2144 (24.3)	39 (25.3)	1.12 (0.76 to 1.65)	
Food allergy§				
No	8119 (91.9)	145 (94.2)	1.00 (referent)	.628
Yes	544 (6.2)	9 (5.8)	1.19 (0.59 to 2.40)	
Asthma§				
No	7411 (83.9)	134 (87.0)	1.00 (referent)	.569
Yes	689 (7.8)	14 (9.1)	1.18 (0.67 to 2.09)	
Hay fever§				
No	6043 (68.4)	111 (72.1)	1.00 (referent)	.278
Yes	1549 (17.5)	34 (22.1)	1.26 (0.84 to 1.89)	
History of autoimmune disease¶				
No autoimmune disease	8356 (94.6)	142 (92.2)	1.00 (referent)	.835
B-cell activation	87 (1.0)	2 (1.3)	1.33 (0.32 to 5.58)	
T-cell activation	387 (4.4)	10 (6.5)	1.29 (0.67 to 2.49)	
Both	4 (0.0)	0 (0.0)		

* CI = confidence interval; OR = odds ratio.

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

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

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

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

¶ Includes self-reported history of specific autoimmune diseases occurring ≥2 y before diagnosis/interview (except the New South Wales study, which did not ascertain date of onset). Autoimmune diseases were classified according to whether they are primarily mediated by B-cell or T-cell responses. 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 scleroderma, and type 1 diabetes.

inverse trends in HCL risk with the frequency, duration, and lifetime consumption of cigarettes in men, although numbers were small in some exposure categories.

Our finding of an association between farming occupation and HCL risk is consistent with the observations of case–control studies published by Oleske et al. (9) (OR = 2.9, 95% CI = 0.9 to 9.9), Clavel et al. (31) (OR = 2.0, 95% CI = 1.1 to 3.5), and Nordström et al. (30) (OR = 2.0, 95% CI = 1.2 to 3.2). However, our study is the first to show a relationship with duration of farming occupation, independently of other exposures such as tobacco smoking.

Participation bias might have contributed to our observation of an inverse association with cigarette smoking if individuals with healthy lifestyles were overrepresented among the controls. However, greater participation of healthier controls might be expected to underestimate cigarette exposure in the source population, because

Table 4. Farming and risk of hairy cell leukemia ("basic model")*

	Controls, N (%)	Cases, N (%)	OR (95% CI)†	*P*
Farming‡				
Ever lived or worked on a farm§				
No	3362 (59.5)	55 (60.4)	1.00 (referent)	.038
Yes	2215 (39.2)	33 (36.3)	1.68 (1.04 to 2.71)	
Ever lived on a farm§				
No	1635 (51.4)	33 (64.7)	1.00 (referent)	.384
Yes	1485 (46.7)	13 (25.5)	1.45 (0.63 to 3.34)	
Ever worked on a farm§				
No	4534 (80.3)	67 (73.6)	1.00 (referent)	.067
Yes	1099 (19.5)	24 (26.4)	1.61 (0.98 to 2.63)	
Occupation as a farmer‖				
Ever worked as a farmer§				
No	4564 (80.8)	67 (73.6)	1.00 (referent)	.089
Yes	1081 (19.1)	24 (26.4)	1.55 (0.95 to 2.53)	
Duration as a farmer§				
Never	4564 (80.8)	67 (73.6)	1.00 (referent)	.184
1–10 y	472 (8.4)	10 (11)	1.32 (0.85 to 3.88)	
>10 y	609 (10.8)	14 (15.4)	1.79 (1.50 to 5.93)	
Ever worked as a mixed animal and crop farmer§				
No	5076 (89.9)	72 (79.1)	1.00 (referent)	.004
Yes	569 (10.1)	19 (20.9)	2.34 (1.36 to 4.01)	
Duration as a mixed animal and crop farmer§				
Never	5076 (89.9)	72 (79.1)	1.00 (referent)	.009
1–10 y	287 (5.1)	8 (8.8)	1.82 (0.85 to 3.88)	
>10 y	282 (5.0)	11 (12.1)	2.98 (1.50 to 5.93)	
P trend			0.025	

* CI = confidence interval; OR = odds ratio.

† OR (95% CI) adjusted for age, sex, race and/or ethnicity, and study.

‡ Self-reported exposure to farming as a residence or work.

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

‖ Exposure measured from self-reported job history.

cigarette smoking is known to cause several types of cancer and such a bias would, thus, attenuate inverse associations with HCL.

The known general concern about health risks associated with cigarette smoking might have led to underreporting of smoking habits among the cases, but recall bias is unlikely to explain the magnitude of risk and the dose–response relationship. Recall bias with respect to farming occupation is also unlikely, because job history is more objective and easier to recall than tasks or contacts with products. However, we still need to be cautious with the interpretation of our results because of the small numbers of subjects in some categories of the quantitative exposures to tobacco smoking (ie, frequency, duration, pack-years) and duration of employment as a farmer.

The homogeneity of the estimates across studies with different control origins (ie, population vs hospitalized) suggests that selection bias, if any, did not play a strong role in our results or cannot be detected due to small numbers.

Although, the biochemical basis of the observed protective effect of smoking on HCL risk is not understood, the role of cigarette smoke could be multifactorial. For example, smoking may alter the activity of metabolic enzymes or compete with other substrates for these enzymes and, thereby, alter the production of toxic endogenous or exogenous metabolites involved in HCL pathogenesis (32). Endometrial cancer, melanoma, and thyroid cancer have also been shown to be inversely associated with cigarette smoking (33–36). If our results for HCL are real, smoking may act through a similar pathway to that hypothesized for endometrial cancer development, via an anti-estrogenic effect, through weight reduction (34) or, possibly, by inhibiting inflammatory reaction as has been proposed for melanoma etiology (35). Indeed, data from recent melanoma studies support the hypothesis that smoking protects melanocytes from the inflammatory reaction induced by long-term ultraviolet radiation (35). Moreover, epidemiological data indicate that smoking might decrease the incidence and/or severity of other inflammatory diseases, including: ulcerative colitis, sarcoidosis, endometriosis, Parkinson's disease, and Sjögren's syndrome (37). Alternatively, as hypothesized for thyroid cancer (36), cigarette smoking may alter sex steroid hormone levels in interaction with specific signaling pathways involved in HCL growth (38). Interestingly, thyroid cancer (papillary), melanoma, and HCL share a common genetic alteration in BRAF-V600E, a signaling pathway that plays a major role in regulating cell survival (39–41). The effect of cigarette smoke on innate, adaptive immunity, or immunomodulation of memory B cells could also play a role in HCL development (37,42).

Two other possible mechanisms for smoking may also be considered. Chemical or biochemical processes may exist by which substances contained in cigarette smoke, such as nicotine or carbon monoxide, exert a protective effect and induce apoptosis. Depending on timing and context, nicotine might act either as a survival factor or as an inducer of apoptosis in normal or transformed lymphocytes (43). Carbon monoxide plays a role in the

Table 5. Sex-specific key findings ("basic model")*

	Male				Female			
	Controls, N (%)	**Cases, N (%)**	**OR (95% CI)†**	***P***	**Controls, N (%)**	**Cases, N (%)**	**OR (95% CI)†**	***P***
History of cigarette smoking‡,§								
No	1640 (33.9)	63 (52.1)	1.00 (referent)	<0.001	2358 (59.0)	20 (60.6)	1.00 (referent)	.553
Yes	3188 (65.9)	58 (47.9)	0.45 (0.31 to 0.65)		1634 (40.9)	13 (39.4)	0.80 (0.39 to 1.67)	
Lifetime cigarette exposure§								
Nonsmoker	1640 (33.9)	63 (52.1)	1.00 (referent)	<0.001	2358 (59.0)	20 (60.6)	1.00 (referent)	.976
1–10 pack-years	793 (16.4)	20 (16.5)	0.68 (0.41 to 1.14)		709 (17.8)	5 (15.2)	0.76 (0.28 to 2.08)	
11–20 pack-years	694 (14.3)	16 (13.2)	0.51 (0.29 to 0.90)		360 (9.0)	3 (9.1)	0.82 (0.23 to 2.83)	
21–35 pack-years	743 (15.4)	13 (10.7)	0.39 (0.21 to 0.71)		361 (9.0)	3 (9.1)	0.79 (0.23 to 2.76)	
>35 pack-years	852 (17.6)	8 (6.6)	0.24 (0.11 to 0.51)		149 (3.7)	1 (3.0)	0.68 (0.09 to 5.18)	
Usual adult height§,‖								
Quartile 1 (low)	917 (26.0)	12 (12.8)	1.00 (referent)	0.029	656 (23.1)	2 (10.0)	1.00 (referent)	.074
Quartile 2	1014 (28.7)	25 (26.6)	1.62 (0.80 to 3.30)		592 (20.9)	3 (15.0)	1.54 (0.25 to 9.43)	
Quartile 3	694 (19.7)	21 (22.3)	1.97 (0.94 to 4.14)		682 (24.0)	10 (50.0)	5.24 (1.09 to 25.19)	
Quartile 4 (high)	810 (22.9)	32 (34.0)	2.78 (1.36 to 5.68)		785 (27.7)	5 (25.0)	2.36 (0.43 to 13.14)	
Farming¶								
Ever lived or worked on a farm§								
No	1786 (58.1)	39 (57.4)	1.00 (referent)	0.068	1576 (61.2)	16 (69.6)	1.00 (referent)	.256
Yes	1250 (40.7)	27 (39.7)	1.68 (0.97 to 2.91)		965 (37.5)	6 (26.1)	1.83 (0.68 to 4.94)	
Occupation as a farmer#								
Ever worked as a mixed animal and crop farmer§								
No	2691 (87.6)	52 (76.5)	1.00 (referent)	0.009	2385 (92.7)	20 (87.0)	1.00 (referent)	.225
Yes	381 (12.4)	16 (23.5)	2.34 (1.29 to 4.26)		188 (7.3)	3 (13.0)	2.36 (0.67 to 8.38)	
Duration as a mixed animal and crop farmer§								
Never	2691 (87.6)	52 (76.5)	1.00 (referent)	0.025	2385 (92.7)	20 (87.0)	1.00 (referent)	.273
1–10 y	194 (6.3)	7 (10.3)	1.93 (0.85 to 4.39)		93 (3.6)	1 (4.3)	1.22 (0.16 to 9.52)	
>10 y	187 (6.1)	9 (13.2)	2.84 (1.32% to 6.10%)		95 (3.7)	2 (8.7)	4.48 (0.93 to 21.54)	

* CI = confidence interval; OR = odds ratio; SES = socioeconomic status.

† Adjusted for age, sex, race and/or ethnicity, study, and SES.

‡ Smoked less than 6 mo or less than 100 cigarettes in lifetime.

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

‖ Height cut points for males (Q1-2: 172; Q2-3: 177.8; Q3-4: 182) and for females (Q1-2: 159; Q2-3: 163; Q3-4: 168).

¶ Self-reported exposure to farming as a residence or work.

Exposure measured from self-reported job history.

Table 6. Exposures associated to hairy cell leukemia risk in the final model*

	OR (95% CI)	*P*
Lifetime cigarette exposure		
Nonsmoker†	1.00 (referent)	.001
1–10 pack-years	0.69 (0.43–1.09)	
11–20 pack-years	0.56 (0.34–0.95)	
21–35 pack-years	0.48 (0.28–0.83)	
>35 pack-years	0.29 (0.14–0.58)	
Ever lived or worked on a farm		
No	1.00 (referent)	.043
Yes	1.70 (1.02–2.82)	
Height‡		
Quartile 1 (low)	1.00 (referent)	.016
Quartile 2	1.60 (0.82–3.12)	
Quartile 3	2.40 (1.23–4.70)	
Quartile 4 (high)	2.59 (1.32–5.07)	

* Adjusted for age, sex, race and/or ethnicity, study, and SES. CI = confidence interval; OR = odds ratio; SES = socioeconomic status.

† Smoked less than 6 mo or less than 100 cigarettes in lifetime.

‡ Height cut points for males (Q1-2: 172; Q2-3: 177.8; Q3-4: 182) and for females (Q1-2: 159; Q2-3: 163; Q3-4: 168).

regulation of the tumor necrosis factor-α pathway involved in cell survival and growth properties of HCL (44).

To our knowledge, the positive association between adult height and HCL has not previously been reported; however, similar associations have been shown in studies of NHL more broadly and leukemia (45), as well as several other cancers (46), suggesting a basic common mechanism (47). Variations in height likely relate to genetic factors and environmental influences acting early in life, such as childhood nutrition, infections, and hormone levels (47).

Although farmers are subject to a variety of exposures (eg, organic antigens, microbial infections, solvents, and pesticides), several published results strengthen the hypothesis that occupational pesticide exposures may be involved in the etiology of HCL, including several pesticide classes, such as organophosphate insecticides in nonsmokers, organochlorine insecticides, and phenoxy and triazine herbicides (17,18,30,48).

Our analyses did not suggest any evidence of risk heterogeneity among sexes that could explain the predominance of HCL incidence among males, although the small number of female cases limited our statistical power in these analyses. Only two previous studies conducted analyses separately for men and women, and both also reported comparable results by sex (10,12). Risk factors more prevalent in men such as farming exposure could explain the difference in incidence between male and female as well as other risk factors not identified in this study. Finally, some portion of the excess risk of HCL among men could be due to factors associated with height, perhaps by influencing the number of proliferating cells and/or other pathways (49).

In conclusion, this pooled analysis of five recent case–control studies from Europe and Australia (16,20–23), supports the hypothesis that farming is associated with HCL risk, and large studies are warranted to elucidate if pesticide exposures or other factors are involved in the relationship. Our findings also bring new evidence that smoking may be inversely related to HCL risk, independent of farming, with a dose–response relationship.

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