

*Short Communication***Occupational Exposure to High Molecular Weight Allergens and Lymphoma Risk Among Italian Adults**

Maria C. Mirabelli,^{1,2,3} Jan-Paul Zock,^{1,2,3} Angelo D'Errico,⁴ Manolis Kogevinas,^{1,2,3,5}
Silvia de Sanjosé,⁶ Lucia Miligi,⁷ Adele Seniori Costantini,⁷ and Paolo Vineis⁸

¹Centre for Research in Environmental Epidemiology, Barcelona, Spain; ²Municipal Institute of Medical Research (IMIM-Hospital del Mar), Barcelona, Spain; ³CIBER Epidemiología y Salud Pública, Spain; ⁴Servizio Regionale di Epidemiologia, Grugliasco, Italy; ⁵Medical School, University of Crete, Heraklion, Greece; ⁶Unit of Infections and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, L'Hospitalet del Llobregat, Spain; ⁷Unit of Occupational and Environmental Epidemiology, ISPO Cancer Prevention and Research Institute, Florence, Italy; and ⁸Environmental Epidemiology, Imperial College London, United Kingdom

Abstract

Objectives. Exposure to high molecular weight (HMW) allergens that provoke immune reactivity through an IgE-mediated pathway has been associated with a decreased risk of B-cell lymphoma. The present analysis was conducted to assess the associations between occupational exposure to specific HMW allergens and the risk of B-cell, T-cell, and Hodgkin's lymphomas.

Methods. We analyzed data from 2,290 incident lymphoma cases and 1,771 population-based controls enrolled in a multicenter study of hematolymphopoietic malignancies conducted in Italy between 1991 and 1993. All cases were histologically or cytologically confirmed. Controls were frequency-matched to cases based on age, sex, and study center. An industrial hygienist evaluated HMW occupational exposure classifications after an asthma-specific job exposure matrix was applied to participants' job histories. Unconditional logistic regression was used to assess associations between occupa-

tional exposures that occurred ≥ 10 years before the date of lymphoma diagnosis and B-cell, T-cell, and Hodgkin's lymphomas.

Results. Ten percent of cases and 11% of controls were occupationally exposed to HMW allergens. Exposed individuals had a decreased risk for all lymphomas combined (odds ratio, 0.78; 95% confidence interval, 0.63-0.97), particularly for B-cell lymphomas (odds ratio, 0.75; 95% confidence interval, 0.59-0.94). The decreased risks for all lymphomas were also observed when HMW allergen exposure was limited to animal and latex allergens.

Conclusions. These findings support the hypothesis that occupational exposure to immunologically active HMW allergens is inversely associated with the risk for lymphoma. The effect of exposure to specific allergens warrants further assessment. (Cancer Epidemiol Biomarkers Prev 2009;18(10):OF1-5)

Introduction

Interest in understanding the relationship between atopy and cancer has increased in recent years. Epidemiologic evidence of an association between factors that compromise the immune system and lymphoma is robust (1-3); however, findings from research conducted to investigate the associations between allergic conditions and lymphoma have not provided clear evidence of an association, and no apparent mechanistic hypotheses have yet emerged. Case reports have described the occurrence of lymphomas among children and young adults with elevated IgE or hyper-IgE syndrome (4, 5), whereas findings from larger epidemiologic studies suggest that allergic disorders may be associated with a decreased risk for non-Hodgkin's

lymphoma (NHL; refs. 6-9), and in particular, that increasing IgE levels might be associated with decreasing NHL risk (8-10). Overall, little is known about how IgE levels affect lymphoma risk and additional investigations are needed to further assess whether the risk may be associated with reactivity to one or more specific allergens.

In the present analysis, we focus on allergen exposures experienced in workplace environments in which exposure to specific allergens is highly dependent on the type of job performed and the industry in which the work takes place. Broadly speaking, inhalation exposures to allergens in occupational settings include plant- and animal-derived proteins and other high molecular weight (HMW) allergens. To investigate the relationship between occupational HMW allergen exposure and lymphoma risk, we used data from a multicenter case-control study of hematolymphopoietic malignancies conducted in Italy between 1991 and 1993. The specific objective of our analysis was to assess the associations between occupational HMW allergen exposure and the risk for B-cell, T-cell, and Hodgkin's lymphomas.

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Requests for reprints: Maria C. Mirabelli, Department of Epidemiology and Prevention, Division of Public Health Sciences, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1063. Phone: 336-716-1112; Fax: 336-713-4157. E-mail: mmirabel@wfubmc.edu

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Materials and Methods

The Italian Multicenter Case-Control Study. Our analyses were conducted using data from a multicenter population-based case-control study conducted in Italy from 1991 to 1993 (11). The study was initially designed and conducted to assess the role of occupational exposure to pesticides and solvents in the incidence of NHL and leukemia, respectively (11-13). Cases ($n = 2,290$), defined as men and women ages 20 to 74 y with newly diagnosed lymphomas, were identified based on their diagnosis at 11 medical centers in Italy. Controls ($n = 1,771$) were frequency-matched to cases based on age (in 5-y categories), sex, and study center. Lymphoma incidence rates in each of the study areas (14) and detailed descriptions of the recruitment, data collection, and cancer subtype identification methods (11, 12, 15) have been previously published. Response and participation refusal rates across study centers and by sex have also been previously published (12, 15). Overall, in 10 centers for which information about response and refusals was available, response rates were 82.5% among cases and 74.2% among controls (15), refusal was higher among controls (overall, 19.4%; 18.9% for males and 19.8% for females) than cases (overall, 10.2%; 10.9% for males and 9.4% for females; ref. 12), and differences across centers in the percentage of eligible respondents interviewed ranged from 65% to 92% among cases and 52% to 95% among controls (15).

Occupational Exposure Assessment. Cases and controls each provided a lifetime occupational history that included a description of the occupation as well as the beginning and ending years of employment for each job held longer than 6 mo (11, 12). Individuals with at least one job listed in their lifetime job histories were classified as having a history of employment (2,127 cases and 1,658 controls). For these individuals, each job was systematically coded using the International Standard Classification of Occupations (16). An asthma-specific job exposure ma-

trix (JEM) was used to assign specific HMW exposures to the job codes (17). The asthma-specific JEM focuses on seven HMW sensitizing agents, as well as HMW bioaerosols, low molecular weight (LMW) sensitizing agents, and other asthma-related exposures. The seven HMW sensitizing agents used by the asthma JEM are those derived from animal proteins, antigenic enzymes, fish, flour and flour-associated antigens, latex, mites and insects, and plants.

Occupational descriptions of jobs that were identified by the asthma JEM as involving exposure to one or more of these HMW allergens were reviewed by an industrial hygienist (A. D'Errico) who was blinded to the case/control status of each individual. According to an a priori protocol, changes from exposure to the relevant HMW agent(s) to nonexposed were considered in order to increase the specificity of the exposure estimates based on the asthma JEM only (17). For example, nurses whose jobs were not hospital-based (e.g., educators) were reclassified as unexposed to latex antigens. The expert assessment resulted in the reclassification of 26 cases and 25 controls from exposed to unexposed.

Cases ($n = 234$) and controls ($n = 208$) with at least one job involving HMW exposures identified by the asthma JEM and confirmed by the industrial hygienist's review were classified as exposed. Participants whose jobs were identified by the JEM or the expert assessment as unexposed to HMW allergens (1,893 cases and 1,450 controls) and participants who had never worked (163 cases and 113 controls) were classified as unexposed. In this analysis, we restricted our definition of exposure to include only the cases and controls whose HMW exposures occurred in jobs held 10 y or more before the date of diagnosis (for cases) or the interview date (for controls). Using this final exposure definition, we classified 222 cases and 197 controls as exposed. We calculated the duration of occupational exposure to HMW allergens using the beginning and ending years of all exposed jobs held, excluding the 10 y prior to the date of diagnosis/interview.

Table 1. Characteristics of the study population according to lymphoma case/control status

	Controls ($n = 1,771$)	Cases ($n = 2,290$)
Age (y)*		
Mean (SD)	54.8 (14.2)	56.3 (14.0)
Median	58.3	60.3
Minimum-maximum	19.6-75.3	18.6-79.2
Sex*		
Female	858 (48.5%)	1,028 (44.9%)
Male	913 (51.6%)	1,262 (55.1%)
Educational attainment		
Primary school or less	941 (53.1%)	1,307 (57.0%) [†]
Secondary school	422 (23.8%)	485 (21.2%)
High school, university or postgraduate diploma	408 (23.0%)	498 (21.8%)
History of employment		
No	113 (6.4%)	163 (7.1%)
Yes	1,658 (93.6%)	2,127 (92.9%)
Occupational HMW allergen exposure		
Never	1,563 (88.3%)	2,056 (89.8%)
Ever	208 (11.7%)	234 (10.2%)
Occupational HMW allergen exposure ≥ 10 y before date of diagnosis	197 (11.1%)	222 (9.7%)
Years of HMW allergen exposure [‡]		
Mean (SD)	31.5 (12.7)	32.6 (12.3)
Median	33	35
Minimum-maximum	2-57	3-56

*Matching variables: age, sex, and study center.

[†]Includes two cases with missing information about educational attainment.

[‡]Duration of exposure values for cases are based on 219 cases with non-missing dates of employment.

Table 2. Associations between occupational exposure to HMW allergens and B-cell, T-cell, and Hodgkin's lymphoma

	No.	No. exposed (%)	OR (95% CI)*
Controls	1,760	197 (11.2)	1.00
All lymphoma cases [†]	2,278	222 (9.7)	0.78 (0.63-0.97)
B-cell lymphoma	1,604	165 (10.3)	0.75 (0.59-0.94)
Chronic lymphocytic leukemia	353	35 (9.9)	0.59 (0.40-0.89)
Diffuse large B-cell lymphoma	525	54 (10.3)	0.77 (0.55-1.07)
Follicular lymphoma	159	15 (9.4)	0.86 (0.48-1.53)
Lymphoproliferative lymphoma (Waldestrom)	119	15 (12.6)	0.87 (0.48-1.57)
Multiple myeloma	270	36 (13.3)	0.90 (0.60-1.37)
Other B-cell lymphoma	178	10 (5.6)	0.45 (0.23-0.89)
T-cell lymphoma	192	20 (10.4)	0.82 (0.49-1.37)
Mycosis fungoides/Sezary	24	4 (16.7)	— [‡]
Other T-cell	168	16 (9.5)	0.76 (0.43-1.34)
Hodgkin's lymphoma	362	22 (6.1)	0.85 (0.52-1.38)
Nodular sclerosis	179	7 (3.9)	0.69 (0.30-1.58)
Other Hodgkin's lymphoma	183	15 (8.2)	0.92 (0.51-1.64)

*Adjusted for age, sex, study center, and educational attainment.

[†]Includes 121 lymphoma cases of unknown type.

[‡]Model did not generate valid estimates.

Statistical Methods. We estimated associations between occupational exposure and case-control status using unconditional logistic regression. Models were adjusted for the three matching variables (age, sex, and study center) and for the level of education attained. Age was classified into five age categories: ≤ 35 , >35 to ≤ 45 , >45 to ≤ 55 , >55 to ≤ 65 , and >65 y. Because of the distinct age distribution of Hodgkin's lymphoma, the models of Hodgkin's lymphoma included age categorized into 10 categories: ≤ 30 , >30 to ≤ 35 , >35 to ≤ 40 , >40 to ≤ 45 , >45 to ≤ 50 , >50 to ≤ 55 , >55 to ≤ 60 , >60 to ≤ 65 , >65 to ≤ 70 , and >70 y. Rather than excluding two cases that lacked information about educational attainment, we assigned these individuals to the education category that included the highest percentage of all cases (primary school education, 52.6%). Associations are presented as odds ratios (OR) and 95% confidence intervals (CI). All analyses were done using SAS version 9.1 (SAS Institute, Inc.).

Following our main analyses, we conducted specific analyses to assess the associations between HMW allergen exposure and specific lymphoma subtypes. In four study centers, multiple myeloma cases were not recruited; as in previous analyses of these data (12), we excluded these four centers from models of multiple myeloma.

We also conducted specific analyses to assess the associations of years of exposure and specific HMW allergens with all lymphomas and with B-cell lymphomas, the most common type of lymphoma in our study population. We then conducted additional analyses using revised exposure definitions in order to assess the effect of two methodologic decisions applied in the process of assigning exposure status: first, the inclusion of individuals without previously held jobs and therefore without the opportunity to be occupationally exposed to HMW, and second, the exclusion of exposures that occurred during the 10 y prior to the date of diagnosis/interview. Finally, we assessed the influence of adjustment of the lymphoma and B-cell lymphoma models for bioaerosol, LMW, and mixed environment occupational exposures.

Results

Table 1 presents the distributions of age and sex for the 2,290 cases and 1,771 control participants from 11 study centers. The highest level of educational attainment, having ever been employed, and occupational exposure to HMW allergens were similarly distributed among the cases and controls. Overall, 10% of cases and 11% of

Table 3. Associations between occupational exposure to HMW allergens and lymphoma cases/control status

Occupational HMW exposure	No. of controls (%)	Lymphoma (all types)		B-cell lymphoma	
		No. of cases (%)	OR (95% CI)*	No. of cases (%)	OR (95% CI)*
Never exposed [†]	1,563 (88.8)	2,056 (90.3)	1.00	1,439 (89.8)	1.00
Years of HMW allergen exposure [‡]					
2 to <30	75 (4.3)	70 (3.1)	0.71 (0.51-1.00)	47 (2.9)	0.66 (0.45-0.96)
30 to <40	59 (3.3)	76 (3.3)	0.89 (0.63-1.27)	59 (3.7)	0.87 (0.59-1.26)
40 to 57	63 (3.2)	73 (3.2)	0.71 (0.50-1.02)	57 (3.6)	0.68 (0.46-0.99)
HMW allergen					
Animal antigens	85 (4.8)	99 (4.3)	0.73 (0.53-0.99)	77 (4.8)	0.71 (0.51-0.99)
Antigenic enzymes	21 (1.2)	27 (1.2)	0.94 (0.52-1.68)	17 (1.1)	0.84 (0.43-1.63)
Fish enzymes	0 (0.0)	1 (<0.1)	—	1 (<0.1)	—
Flour-associated antigens	33 (1.9)	38 (1.7)	0.82 (0.51-1.32)	24 (1.5)	0.69 (0.40-1.19)
Latex antigens	30 (1.7)	20 (0.9)	0.53 (0.30-0.95)	15 (0.9)	0.55 (0.29-1.05)
Mite and insect allergens	56 (3.2)	64 (2.8)	0.82 (0.56-1.19)	46 (2.9)	0.73 (0.48-1.09)
Plant-associated antigens	6 (0.3)	14 (0.6)	1.69 (0.64-4.44)	12 (0.7)	1.89 (0.70-5.12)

*Adjusted for age, sex, study center, and educational attainment.

[†]Never exposed = referent category for all models shown in the table.

[‡]Categories of duration are tertiles of the exposure distributions of the exposed case population. Cases with missing duration ($n = 3$) were excluded from this analysis.

controls were occupationally exposed to at least one HMW agent 10 or more years before their date of lymphoma diagnosis, and within this exposed population, the mean number of years in HMW-exposed jobs was similar for cases and controls.

Occupational exposure to HMW allergens was associated with a decreased risk for all lymphomas (OR, 0.78; 95% CI, 0.63-0.97) and of B-cell lymphomas (OR, 0.75; 95% CI, 0.59-0.94) in particular (Table 2). Nonstatistically significant decreased risks were also observed for individual B-cell lymphoma subtypes, as well as for T-cell lymphoma and Hodgkin's lymphoma. When we restricted our study population to the 2,127 cases and 1,658 controls who reported having one or more jobs in their job histories, we observed negligible changes in the decreased risks for all lymphomas (OR, 0.79; 95% CI, 0.64-0.97), and specifically for B-cell lymphomas (OR, 0.76; 95% CI, 0.60-0.95). And the results are also consistent with what we observed when the definition used to categorize individuals as exposed was expanded to include any occupational exposure to HMW allergens that occurred in any job in a participant's history (i.e., ever versus never): e.g., all lymphomas (OR, 0.79; 95% CI, 0.65-0.98) and B-cell lymphomas (OR, 0.74; 95% CI, 0.59-0.93). Additional adjustment for bioaerosol, LMW, and mixed environment exposures generated ORs of 0.83 (95% CI, 0.66-1.03) for all lymphoma types and 0.78 (95% CI, 0.61-0.98) for B-cell lymphomas. When we examined the lymphoma and B-cell lymphoma associations across tertiles of exposure duration, no clear duration-responses emerged (Table 3). Exploratory assessment of the role of exposure duration in the associations observed for chronic lymphocytic leukemia, the B-cell lymphoma subtype with the strongest inverse association (Table 2), yielded a stronger and statistically significant inverse association among those with <30 years of HMW allergen exposure (OR, 0.25; 95% CI, 0.09-0.71), than among those with 30 to <40 years (OR, 0.77; 95% CI, 0.41-1.48) or 40+ years of exposure (OR, 0.67; 95% CI, 0.38-1.18).

Only one case and no controls reported occupational exposure to fish antigens, one of the seven HMW allergens categorized by the asthma JEM and the expert review. Associations between the remaining six HMW allergens and lymphoma case/control status were consistent with the ORs generated using the variable indicating exposure to any of the allergens. These analyses generated inverse and statistically significant risks for exposure to animal antigens (OR, 0.73; 95% CI, 0.53-0.99) and latex antigens (OR, 0.53; 95% CI, 0.30-0.95; Table 3). The finding of decreased risk for B-cell lymphomas associated with HMW exposures persisted when the exposure was limited to exposure to animal antigens (OR, 0.71; 95% CI, 0.51-0.99). In general, however, we were unable to generate estimates of the associations between specific allergens, including duration of exposure to specific allergens, and lymphoma subtypes because of the limited number of exposed cases and controls.

Discussion

Our results suggest that occupational exposure to HMW sensitizing agents is associated with a decreased risk of lymphoma, particularly with chronic lymphocytic leukemia, one of the more common B-cell lymphoma subtypes in our study population. These findings are generally con-

sistent with the associations reported in a similar lymphoma case-control study conducted in Spain (18), and further suggest a possible role for animal and latex exposures. In combination with previous evidence of decreased NHL risk associated with allergies to foods, plants, mold and animals, bee and wasp stings, vaccinations, and inoculations for allergies and asthma (19), our data support the hypothesis that chronic stimulation of the immune system by exogenous antigenic exposures may be associated with a reduced risk of developing NHL.

Our findings are strengthened by the large study population, lifetime job histories provided by each of the participants, and review of occupational exposure assignments by an experienced industrial hygienist. Participants' job histories included beginning and ending years of employment in each job, allowing us to calculate the duration of occupational exposure to HMW allergens. However, our analyses of the associations between exposure duration and lymphoma case/control status did not generate clear evidence of a duration-response trend. If applying an asthma JEM that was developed relatively recently introduced misclassification of exposure differentially across time—that is, if the asthma JEM misclassified jobs held decades ago more often than those held recently—then attenuation of the effect estimate with increasing duration of exposure would be unsurprising. If, in fact, a longer duration of HMW allergen exposure is associated with a decreased risk of lymphoma and misclassification of exposure is increased with time since the jobs were held, then the inconclusive duration-response trend observed in these data is also unsurprising. More information about changes over time, exposure intensity, use of ventilation or personal protective equipment, and other behaviors and/or features of the work environment would improve our ability to appropriately characterize long-term and older exposures, such as those often reported in lifetime job histories. In the present study, an industrial hygienist reviewed the lifetime job history if any of the jobs reported were identified by the asthma JEM as involving exposure to HMW allergens. This improvement in exposure classification effectively reduced the number of individuals who may have been incorrectly identified as exposed, according to the asthma JEM. This reduction in misclassification is also expected to have reduced the resulting bias towards unity. The expert assessment did not, however, include an evaluation of the intensity of occupational exposure to HMW allergens or a review of bioaerosol, LMW, mixed environment, or other asthma-related exposures. Although the final results were adjusted for age, sex, study center, and educational attainment, they were not adjusted for these other related exposures or for occupational and environmental lymphoma risk factors.

We were able to assess the risks of specific lymphoma types and of six of the seven HMW allergens. The small number of mycosis fungoides/Sezary lymphoma cases ($n = 24$) prohibited us from generating valid risk estimates while adjusting our statistical models for the three study design variables: age, sex, and study center. Without adjustment for study center, the resulting estimate suggests an elevated risk of mycosis fungoides/Sezary lymphoma (OR, 1.60; 95% CI, 0.53-4.87); this estimate is based on four exposed cases and should be interpreted with caution.

Investigation of our hypothesis in study populations with larger numbers of lymphoma cases, especially T-cell and Hodgkin's lymphoma cases, may be a worthwhile step towards clarifying the specificity of the relationship between HMW allergen exposures and lymphoma risk. In particular, analysis of our hypothesis in larger study populations and populations with information about atopic status would allow investigation of the roles of atopy and sex. In our analyses, HMW allergen exposure was more strongly associated with lymphoma risk in men than in women (data not shown), but the small numbers of exposed individuals with specific lymphoma subtypes prohibited thorough investigation of effect modification by sex.

The similar percentages of individuals who reported jobs with HMW allergen exposures, the mean number of years with exposure, and the number of exposed jobs together suggest that recall and/or reporting bias may not have strongly affected our results. Similarly, the inverse associations observed in these data are not consistent with the expected effect of these biases. Nonetheless, if cases were more likely to recall or report jobs involving exposures, including HMW allergen exposures, that potentially affect their health, then the true difference between cases and controls in the prevalence or duration of exposure may have been even larger, and the ORs reported herein may be higher and closer to null value than the true associations. Indeed, using these data, we were unable to assess whether our data may have been affected by the tendency for healthy workers to continue working in exposed jobs (i.e., the healthy worker effect), the extent to which healthy individuals are hired into more or less exposed jobs, or the extent to which refusal to participate was correlated with occupational status and/or HMW allergen exposure. We were also unable to assess whether individuals who were occupationally exposed to HMW allergens may have experienced other similar or highly correlated occupational exposures, whether they may have experienced lower levels of other factors that increase the risk of lymphoma, whether information about combinations of exposures may increase or attenuate the estimates of association generated in these analyses, or whether differences in exposure status may be attributed to any of the numerous unmeasured characteristics, including ethnicity, urban versus rural residence, and other nonoccupational exposures.

Overall, our findings suggest that occupational exposure to HMW sensitizing agents is inversely associated with the risk of lymphoma. These findings also suggest a role for specific HMW allergen exposures. Whether occupational exposure to animal and latex allergens in particular, duration of the specific exposures, or the age at which the exposure began affect lymphoma risk should be more thoroughly assessed in studies of large and diverse populations for which detailed information about individual job history is available. Further investigation of these hypotheses may yield additional information about exposure dose and susceptibility useful for generating and refining hypotheses about the physiologic pathway between allergen exposure, atopic status, IgE level, and lymphoma risk. Currently, the mechanism by which HMW exposure may reduce lymphoma risk remains unclear. Whether long-term HMW allergen exposure and the resulting chronic immune stimulation leads to a reduction

in lymphoma risk by suppressing antigen-driven lymphocyte accumulation, stimulating lymphocytes that may be effective against tumor cells, or as a consequence of the chronically elevated levels of WBC and specific IgE antibodies warrants further assessment. Information about atopic sensitization and regulation of the IgE-mediated pathway, history of immunotherapy, and an assessment of whether HMW antigen-sensitized individuals avoid work-related HMW exposures will improve future epidemiologic research regarding this hypothesis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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