Short Communication

Occupational Exposure to Immunologically Active Agents and Risk for Lymphoma

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Abstract

Objectives: **We evaluated whether occupational exposure to high molecular weight agents that are associated with asthma and that act predominantly through an immunoglobulin E (IgE)–dependent hypersensitivity mechanism is also associated with risk for specific lymphoma types.**

Methods: **The Spanish lymphoma case-control study includes 519 newly diagnosed cases of lymphoid neoplasms and 554 hospital controls ages 20 to 80 years. Lymphomas were histologically or cytologically confirmed and classified according to the WHO classification. Lifetime occupational exposure to seven high molecular weight agents such as latex was evaluated through an asthma-specific job-exposure matrix and validated by an industrial hygienist. Odds ratios (OR) and 95% confidence intervals (95% CI) were adjusted for age, sex, hospital, and occupational exposures.**

Results: **Subjects exposed to high molecular weight agents had an increased risk for Hodgkin's lymphoma (OR, 2.27; 95% CI, 0.93-5.50), particularly nodular sclerosis (OR, 3.22; 95% CI, 1.14-9.09). ORs did not increase with duration of exposure to these agents. Exposure to high molecular weight agents was not associated with risk of other B-cell lymphomas; for most specific subcategories of B-cell lymphoma, ORs were below unity. A slightly increased OR (95% CI) was seen for mycosis fungoides [1.60 (0.53-4.84)], although overall there was no increased risk for T-cell lymphomas.**

Conclusions: **Exposure to immunologically active agents among clinically immunocompetent subjects was associated with risk for Hodgkin's lymphoma.** (Cancer Epidemiol Biomarkers Prev 2004; 13(11):1814–8)

Introduction

The role of the immune system in the etiology of lymphomas has been shown by the excess risk among immunosuppressed patients as well as in situations of chronic immunostimulation due to bacterial and viral infections. A small decreased risk of predominantly non–Hodgkin's lymphoma has been observed among asthma patients in several studies, suggesting an immunologic link between both diseases (1, 2). In contrast, increased levels of IgE and soluble CD23, a molecule characteristic of T-helper type 2 (T_H2) immune responses, were seen to be associated with the development of AIDS-non–Hodgkin's lymphoma in prospective nested case-control studies carried within a large AIDS cohort study (3, 4). In addition to this, a history of atopy was seen to be associated with elevated soluble CD23 in those who developed AIDS-non–Hodgkin's lymphoma (4). The predominant immunologic T_H2 response observed in classic Hodgkin's lymphoma (5) is similar to that following exposure to agents associated with the development of asthma (6). Asthma is typically associated with a deregulated, T_H2-biased immune response including the production of B-cell-stimulatory cytokines such as interleukin-4 and -13. Several occupations have been associated with lymphomas, but findings for specific exposures are inconsistent (7, 8). We evaluated whether occupational exposure to high molecular weight agents that are associated with asthma (9) and that act predominantly through an IgE-dependent hypersensitivity mechanism (10) is also associated with risk for specific lymphoma types.

Materials and Methods

The design and results of the Spanish lymphoma case-control study have been described previously (11).

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Note: This case-control study was undertaken within the framework of the EPILYMPH international study. Part of this work was done while M. Kogevinas and S. de Sanjose were on sabbatical at the National Cancer Institute (Bethesda, MD).

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Briefly, newly diagnosed cases of lymphoid neoplasms and hospital controls were recruited during 1998 to 2002 from four Spanish hospitals (response rate, 84.4% cases and 96.4% controls). The diagnosis of lymphoma was verified by histology and 99% of them were supplemented by immunohistochemistry test and flow cytometry. Diagnosis of chronic lymphocytic leukemia was based on cytology and flow cytometry. Cases were categorized according to the WHO Classification for Neoplastic Diseases of the Lymphoid Tissues (ref. 12; Table 1). Subjects with a diagnoses of uncertain malignant potential such as post-transplant lymphoproliferative disorder or monoclonal gammapathies of undetermined significance were excluded. Controls were frequency matched to cases by age, sex, and hospital and were selected from admission lists, excluding hospitalizations for organ transplant, systemic infection, or severe immunosuppression. Controls hospitalized for respiratory diseases were excluded from this analysis. We further excluded 26 cases and 1 control that were either diagnosed with HIV infection or had an organ transplant. The final study population includes 519 cases and 554 controls ages 20 to 80 years with complete occupational history. All participants provided written informed consent in accordance with guidelines from the institutional review boards of the participating institutes.

Information was requested through a structured face-to-face interview on sociodemographic, reproductive, familial, and medical histories including allergies and asthma, residence, tobacco, alcohol and drug consumption, use of hair dyes, sun exposure, and complete occupational history. We evaluated lifetime occupational history for all jobs with >1-year duration as well as nonemployed periods. Occupations were coded by an industrial hygienist using the *International Standard Classifications of Occupations*-68 system (13) and these codes were linked to an asthma-specific job-exposure matrix (JEM; ref. 14).

Table 1. Description of the study population, *n* (%)

	Controls (n = 554)	Cases (n = 519)
Sex, women	264 (48)	232 (45)
Age, mean (SD)	57.0 (16.2)	58.9 (15.6)
Reported asthma	53 (10)	35 (7)
Social class		
Unclassified	197 (36)	166 (32)
Professionals	15 (3)	23 (4)
Skilled manual and nonmanual	79 (14)	87 (17)
Unskilled manual	263 (48)	243 (47)
Occupational exposures*		
Exposure to high molecular weight (IgE-mediated acting) agents	87 (16)	82 (16)
Exposure to low molecular weight agents	184 (34)	157 (30)
Exposure to bioaerosols	145 (26)	158 (31)
Mixed exposures	235 (43)	251 (48)
Exposure to other possible asthmagens	287 (52)	280 (54)
Lymphoma cell lineage		
B-cell		416 (80)
Hodgkin's		59 (11)
T-cell		44 (9)

*Subjects could be classified in more than one category. Five controls and one case could not be assigned to any occupational category.

The asthma JEM evaluates 22 occupational exposures of which 18 are characterized as ''high risk'' for asthma. The starting point for defining asthma risk was a list of >150 chemical and biological substances stratified into high and low molecular weight agents (15). This list was completed and updated. The differentiation between high and low molecular weight agents is arbitrary but has been extensively used in occupational asthma epidemiology and diagnosis and, to a large extent, is related to different mechanisms of action. The scheme followed in the JEM is hierarchical, with a few specific agents (e.g., latex and isocyanates) nested within larger groups. Both specific agents and mixed environments are evaluated. Each matrix cell contains a yes or no indication of exposure. The matrix favors specificity over sensitivity, and jobs are classified as exposed only if the probability of exposure is expected to be high for a considerable number of subjects in that job. The matrix also contains a category termed ''needs individual reevaluation'' for job codes considered that could benefit from a detailed evaluation of the textual job history by an expert (e.g., jobs for which exposures could differ greatly by industry).

Finally, the complete occupational history of all subjects classified as exposed is evaluated case-by-case by an expert. Seven of the exposures evaluated are high molecular weight agents that are protein-derived agents causing sensitization through an IgE-mediated mechanism. These agents are derived from plants (latex, flour, and other), animals (rodents, livestock, fish, and shellfish), biological enzymes, and mites that are known to produce asthma through an IgE-mediated mechanism. The JEM evaluates six low molecular weight agents that include a variety of organic and inorganic compounds that have not been consistently associated with an IgE-mediated mechanism: highly reactive chemicals (isocyanates, anhydrides, etc.), isocyanates as a separate exposure, sensitizing drugs, industrial cleaning agents, wood dusts, and metal sensitizers and fumes. The matrix also includes bioaerosols (moulds and endotoxins) and four mixed environments that have been associated with asthma (metal working fluids, irritant gases or fumes with moderate to high probability of accidental or periodic exposure to very high levels, exposures in textile, and agriculture with exposure to organic particles).

Finally, it includes three wide groups of agents that are not typically associated with asthma (low-level exposure to irritants, exposure to passive smoking, and fumes) and a large nonexposed group. Detailed occupational information for 174 subjects identified by the JEM as exposed to high molecular weight agents was reevaluated by an industrial hygienist (J.P.Z.), blindly as to case-control status, and 22 subjects were reclassified as nonexposed.

Unconditional logistic regression was used to estimate odds ratios (OR) for the different lymphoma categories and the corresponding 95% confidence interval (95% CI) using the statistical package Stata version 8.0. All models evaluating exposure to high molecular weight agents were adjusted for the matching variables age (in 5 groups; 10 groups for Hodgkin's lymphoma due to the bimodal age pattern), sex, and area (three hospitals) and for the remaining four categories of occupational exposures evaluated by the matrix (low molecular weight agents,

bioaerosols, mixed exposures, and other possible asthma-related exposures). Analyses in other populations have shown that workers may be exposed to more than one asthma-related occupational agent (9) and adjustment for all occupational exposures was kept in the final models irrespective of statistical significance or degree of modification of the ORs (16). Adjustment for prior asthma attacks and for socioeconomic status did not modify ORs and were not included in the final models.

Results

Table 1 describes the characteristics of the study population in relation to age, sex, social class, history of asthma, grouping of lifetime occupational exposures, and lymphoma cell lineage. The average age of the study population was 58.9 years for cases and 57 years for controls. Men were slightly more common than women. Social distribution of cases and controls was similar, and 10% of the controls and 7% of the cases reported ever been treated for asthma. Cases were slightly more likely to be exposed to bioaerosols, mixed exposures, and other possible asthmagens. B-cell lymphomas were the commonest category.

Among controls, the risk of asthma diagnosed at least 1 year before hospitalization was associated with exposure to high molecular weight agents (OR, 1.64; 95% CI, 0.78-3.47) and low molecular weight agents (OR, 1.45; 95% CI, 0.79-2.66), although results were not statistically significant.

Table 2 describes the risk of lymphoma types associated with exposure to high molecular weight agents. Subjects exposed lifetime to high molecular weight agents had an increased risk for Hodgkin's lymphoma (OR, 2.27; 95% CI, 0.93-5.50), with higher OR (95% CI) found for nodular sclerosis [3.22 (1.14-9.09)] than for other Hodgkin's lymphoma subtypes (e.g., mixed cellularity). Exposure to high molecular weight agents was not associated with risk of other B-cell lymphomas; for most specific subcategories of B-cell lymphoma, ORs were below unity. For chronic lymphocytic leukemia and diffuse large B-cell lymphoma, long duration of exposure to high molecular weight was associated with lower ORs ($P = 0.067$, test for linear trend for diffuse large B-cell lymphoma). A slightly increased OR (95% CI) was seen for mycosis fungoides [1.60 (0.53-4.84)], although overall there was no observed risk for T-cell lymphomas.

For Hodgkin's lymphoma diagnosed before age 50 years, exposure to high molecular weight was associated to a 3-fold risk as compared with nonexposed subjects (Table 3). A weaker association was observed for subjects ages ≥50 years. Risk did not increase with duration of exposure (OR, 2.29 for 1-5 years of exposure to high molecular weight agents compared with nonexposed; OR, 2.21 for >5 years; $P > 0.05$, test for linear trend). Exposure to high molecular weight agents among Hodgkin's lymphoma cases occurred in several occupations including nurses exposed to latex, animal production workers exposed to animal proteins, house dust mite in domestic cleaners, and bakers exposed to flour among others. An analysis of specific high molecular weight agents did not indicate a predominance of any specific agent associated with the increased risk. Exposure to other occupational agents evaluated by the JEM such as bioaerosols and low molecular weight agents (Table 3) was not associated with risk for Hodgkin's lymphoma.

Table 2. ORs and 95% CIs for occupational lifetime exposure to high molecular weight agents (IgE mediated) and type of lymphoma in Spain

	No. subjects* exposed/ nonexposed	OR† (95% CI)
Controls	79/470	Reference
All lymphomas	69/449	0.84 (0.58-1.23)
Hodgkin's lymphoma	9/50	2.27 (0.93-5.50)
Nodular sclerosis	7/32	3.22 (1.14-9.09)
Lymphocyte predominance, mixed cellularity, not otherwise specified	2/18	0.97 (0.20-4.93)
B-cell lymphomas	53/362	0.75 (0.50-1.12)
Chronic lymphocytic leukemia	15/98	0.65 (0.33-1.25)
Lymphoplasmacytic lymphoma	1/15	0.39 (0.05-3.20)
Splenic marginal zone lymphoma	6/17	1.79 (0.57-5.62)
Plasma cell myeloma	12/65	0.90 (0.44-1.85)
Marginal zone B-cell lymphoma	3/25	0.94 (0.25-3.55)
Follicular lymphoma	7/35	1.04 (0.41-2.65)
Diffuse large B-cell lymphoma	7/79	0.46 (0.19-1.09)
Other B-cell lymphoma	2/28	0.45 (0.10-2.05)
T-cell lymphoma	7/37	0.83 (0.33-3.76)
Mycosis fungoides/Sezary	6/16	1.60 (0.53-4.84)
Other T-cell	1/21	0.21 (0.03-1.66)

*Five controls and one case could were excluded because of missing data on occupational exposure category.

†Each lymphoma subgroup is compared with all controls, ignoring in each model all other types of lymphoma. ORs are adjusted for age (in 5 groups; 10 groups for Hodgkin's lymphoma due to the bimodal age pattern), sex, area (three hospitals), and four other occupational exposure groups (low molecular weight agents, bioaerosols, mixed exposures, and other possible asthma-related exposures).

An attack of asthma diagnosed at least 1 year before hospitalization was associated to OR <1 for all lymphomas (OR, 0.67; 95% CI, 0.43-1.05) and B-cell lymphomas (OR, 0.60; 95% CI, 0.36-0.99) and to a lesser extent for Hodgkin's lymphoma (OR, 0.79; 95% CI, 0.30-2.09). An OR >1 was seen for T-cell lymphomas (OR, 1.12; 95% CI, 0.37-3.38). Among asthmatics, exposure to high molecular weight agents was associated with a high OR (95% CI) for Hodgkin's lymphoma [17.8 (0.73-434)], but this was based on small numbers (11 exposed subjects). The OR (95% CI) for nonasthmatics was 1.74 (0.70-4.34) and the interaction term between exposure to high molecular weight agents and asthma was not statistically significant ($P = 0.29$).

Discussion

High molecular weight agents that are known to stimulate the immune system through an IgE-mediated pathway were associated with risk for Hodgkin's lymphoma. The mechanism of antibody-dependent hypersensitivity and asthma is complex (10, 17). High molecular weight agents are complete antigens and

Table 3. ORs and 95% CIs for Hodgkin's lymphoma and occupational lifetime exposure to high molecular weight agents (IgE mediated) by age, sex, duration of exposure, and exposure to other occupational agents

	Cases (*n*)	Controls (*n*)	OR* (95% CI)
Age at onset of lymphoma (y)			
≤50			
Nonexposed	17	161	1.0
Exposed	4	35	3.02 (0.72-12.7)
>50			
Nonexposed	15	276	1.0
Exposed	5	15	1.80 (0.55-5.84)
Duration of exposure to high molecular weight agents (y)			
Nonexposed	50	470	1.0
≤5	4	24	2.29 (0.66-7.98)
>5	5	55	2.21 (0.75-6.53)
Exposure to other occupational agents†			
Low molecular weight agents	16	184	0.73 (0.38-1.43)
Bioaerosols	6	145	0.50 (0.16-1.54)
Mixed environments	15	235	1.10 (0.49-2.49)
Other possible asthmagens	33	287	1.26 (0.68-2.34)

*ORs are adjusted for age (10 age groups; 5 age groups in some models due to problems in model convergence), sex (when appropriate), area (three hospitals), and other occupational exposures in four groups (low molecular weight agents, bioaerosols, mixed exposures that include mainly metal working fluids and agriculture, and possible asthma-related exposures such as environmental tobacco smoke).

† Low molecular weight agents include highly reactive chemicals (isocyanates, anhydrides, etc.), sensitizing drugs, industrial cleaning agents, wood antigenic dusts, and metal sensitizers. Bioaerosols include moulds and endotoxins. Mixed environments include metal working fluids, agriculture with high probability of exposure to organic particulate or fumes, textile industry, and irritants. Possible asthmagens include low-level exposure to irritants, exhaust fumes, passive smoking, and low-level exposure to several other chemical agents. Reference category are nonexposed to each category.

cross-link with surface-bound IgE, leading to a cascade of events and eventually to an inflammatory response. Several inflammatory mediators (e.g., interleukin-3, -4, and -5 cytokines and β-chemokines) are involved in this process. The mechanism underlying the association between exposure to high molecular weight agents and Hodgkin's lymphoma may be directly related to the nature of T_H2 responses, which are characterized by B-cell lymphocyte activation, and may provide a favorable environment for the growth and survival of Reed-Sternberg cells (5). Reed-Sternberg cells are the neoplastic cells that characterize Hodgkin's lymphoma, are primary secretors of cytokines and chemokines, and are typically surrounded by an extensive lymphocyte inflammatory response (12). It is interesting to note that the nodular sclerosis subtype of Hodgkin's lymphoma, which is associated with a lower frequency of EBV infection than the mixed cellularity subtype (18), was most clearly associated with exposure to high molecular weight agents and, by inference, to a T_H2 immune environment. This is consistent with the notion that chronic T_H2 immune stimulation led to ongoing B-cell activation, which resulted in a greater probability for the occurrence of genetic lesions that contribute to the genesis of this subtype of Hodgkin's lymphoma.

The advantage of using an asthma-specific JEM is the evaluation of a group of agents that occur in a variety of jobs that have little in common. To increase specificity of exposure classification, the asthma JEM was coupled with expert assessment through a detailed evaluation of each job, industry, and tasks of persons identified through the JEM as exposed to high molecular weight agents. A limitation in this analysis is that we evaluated only exposures associated with asthma, whereas other exposures that also act through immunologic mechanisms in diseases such as atopic dermatitis or atopic rhinitis were not included. This could be particularly of interest for the evaluation of mycosis fungoides or non–Hodgkin's lymphoma, respectively. In addition, some low molecular weight agents such as acid anhydrides and platinum salt act as haptens and have been associated with occupational asthma and the production of specific IgE. However, the presence of hapten-reactive IgE is only documented among few subjects exposed to these agents (17).

Information on occupation and on asthma were obtained at the time of subjects recruitment; therefore, our estimates are based on a retrospective assessment of exposure. To account for a minimal latency period, only those exposures that took place at least 12 months before the diagnosis were included in the analysis. Our case-control study was based on hospitalized patients with high participation rates for both cases and controls. A bias in our estimates could take place if some occupations or medical conditions affected hospitalization rates. Because this is highly probable for asthma, we were very cautious to exclude those patients that were hospitalized at the time of the study for asthma or related diseases or that reported a hospitalization related to asthma during the 12 months before the inclusion period. The resulting prevalence of ever asthma among our control population (10%) was similar to that observed in other large population series (19). We did not exclude any subject based on occupation, assuming no differential hospitalization rates by occupation. Furthermore, the basis of the analysis was exposure to specific agents that could occur in a variety of different occupations unlikely to have a common hospitalization referral pattern.

The approach followed in this analysis allowed an evaluation of the role of the immune system in the etiology of lymphomas among subjects that were clinically immunocompetent and provided clues for the association of occupational exposures and lymphomas.

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