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Occupational exposure to immunologically active agents and risk for lymphoma: The European Epilymph case–control study

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ABSTRACT

Objectives: Allergies and asthma may be protective for the development of lymphoma. We evaluated whether occupational allergens that provoke immune reactivity and asthma through an IgE-mediated pathway are protective for lymphoma.
Methods: The Epilymph study includes histologically or cytologically confirmed Hodgkin, B-cell, and T-cell lymphoma cases from six European countries (Spain, France, Germany, Italy, Ireland, and Czech Republic) recruited in 1998–2004. Controls were frequency matched to cases by age, gender, and study centre. Lifetime occupational exposure to seven high molecular weight (HMW) agents was evaluated through an asthma-specific job-exposure matrix. 2205 lymphoma cases and 2296 controls with complete occupational history could be included in the analysis. Associations between HMW exposures and lymphoma were evaluated using pooled unconditional logistic regression analyses.
Results: Individuals exposed to HMW agents had a non-statistically significant decreased risk of any lymphoma (OR, 0.88: 95% CI, 0.74–1.05) and of B-cell lymphoma (OR, 0.91; 95% CI, 0.76–1.09), and a significantly decreased risk for Hodgkin lymphoma (OR, 0.62; 95% CI, 0.40–0.98). A decrease in risk for lymphoma was found for exposure to latex (OR, 0.74; 95% CI, 0.55–0.99).
Conclusions: Further epidemiologic and mechanistic research is needed to confirm that occupational exposure to HMW agents predisposing to asthma can reduce the risk of lymphoma.

1. Introduction

The role of the immune system in the aetiology of non-Hodgkin lymphoma (NHL) has been demonstrated by the excess risk among immunosuppressed patients and also in situations of chronic immunostimulation, due to bacterial and viral infections [1]. A decreased risk of haematological malignancies has been observed among asthma patients in several studies suggesting

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an immunological link between both diseases [2–8]. Atopic asthma is typically associated with a deregulated Th2-biased immune response including the production of B cell-stimulatory cytokines, such as IL-4 and IL-13 [9,10]. Asthma is associated with high IgE levels. Interestingly, total and specific IgE to common aeroallergens have been shown to be inversely associated with risk of lymphoma in some studies [11]. However, the fact that in a small prospective study this association was observed close to the time of diagnosis, was interpreted as a possible reverse causality in which NHL suppresses the immunologic response to allergens [12]. Some case–control studies have suggested a link between asthma and lymphoma, but the potential concern in these studies is that the onset of the disease may change IgE levels.

In a preliminary analysis of the Spanish arm of the international Epilymph case–control study on lymphoma, we evaluated whether occupational exposure to high molecular weight (HMW) agents that are associated with asthma [13] and that act predominantly through an IgE-dependent allergic mechanism [14], were also associated with risk for specific NHL types [15]. That analysis showed that exposure to HMW agents may lead to a decreased risk of all lymphomas, particularly B-cell lymphoma, and to an increased risk for Hodgkin lymphoma. In 2009, a large case–control study in Italy using a similar approach also identified a reduced risk of lymphoma associated with exposure to agents related to occupational asthma [16].

In this analysis we incorporate data from studies in six countries participating in the international Epilymph consortium following the same protocol. We evaluated whether lifetime occupational exposure to HMW agents capable of inducing IgE-mediated allergic sensitization is associated with the risk of specific lymphoma subtypes [17], aiming to reduce with this analysis the potential effect of a reverse causality mechanism.

2. Materials and methods

2.1. Study design and participants

The Epilymph study is a multicenter case–control study including populations from 6 European countries (Germany, Italy, Spain, Ireland, France and Czech Republic). Newly diagnosed cases of lymphoid neoplasms and controls were recruited from 1998 to 2004 using a common core protocol and interview in all countries. The diagnosis of lymphoma was verified by histology and 99% of them were supplemented by immunohistochemistry test and flow cytometry. Cases were categorized according to the WHO Classification for Neoplastic Diseases of the Lymphoid Tissues [18]. Subjects with a diagnosis of uncertain malignant potential such as post-transplant lymphoproliferative disorder or monoclonal gammapathies of undetermined significance were excluded. Controls were identified at same time as the diagnosis of the cases and were sampled from the general population based on census lists in Italy and Germany matched by age and sex. In the other 4 countries, controls were recruited from the same hospital as the cases and were frequency matched to cases by age, gender, and hospital. Individuals with organ transplantation, HIV or a diagnosis of a systemic infection were excluded by protocol [19,20]; for our study, controls hospitalized due to respiratory diseases were also excluded. We further excluded subjects who reported to have never worked. Finally, the study includes 2205 lymphoma cases and 2296 controls with complete information of the exposure and adjustment variables (Fig. 1). Informed consent was obtained from all participants in accordance to guidelines from the institutional review boards of the participating institutes.

2.2. Questionnaire and occupational history

Information was requested through a structured face-to-face interview. The same structured questionnaire was used and translated into the local language in each country. Questions collected information on socio-demographic factors, reproductive, familial and medical history including allergies and asthma, residence, tobacco, alcohol and drugs consumption, use of hair dyes, sunlight exposure and complete occupational history. Lifetime occupational history was recorded including all jobs held for at least one year including a job and industry description and start and end years.

2.3. Occupational exposure assessment

Occupations were coded in each country using the 1968 International Labour Office International Standard Classification of Occupations (ISCO-68) [21]. ISCO-68 uses a five-digit hierarchical system that classifies jobs into 1506 occupational titles and is published in English, French, and Spanish. Codes of all jobs for each participant were linked to an asthma-specific job exposure matrix (OAJEM) that had been adapted to the ISCO-68 coding system [15]. The OAJEM includes protein exposures such as latex, flour, biological enzymes and mites that are known to produce asthma through an IgE mediated mechanism [13]. In addition, the OAJEM also assigns exposure to other recognized occupational risk factors for asthma. Each matrix cell contains a yes or no indication of exposure, favouring specificity over sensitivity as 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. Seven of the protein-derived HMW included in the OAJEM are agents causing sensitization through an IgE-mediated mechanism. These agents are classified in a hierarchical scheme with some specific allergens nested in the larger groups: latex, flour, other plant antigens (derived from plants); rodents and livestock, fish and shellfish (derived from animals); arthropods or mites; and bioaerosols. These agents are known to produce asthma through an IgE mediated mechanism. The OAJEM also evaluates low molecular weight agents that include a variety of organic and inorganic compounds that have not been consistently associated with an IgE-mediated mechanism such as isocyanates, metal fumes and wood dusts, bioaerosols including moulds and endotoxins and four mixed environments that have been associated with asthma (metal working fluids, textile and agricultural settings). Finally, the OAJEM includes three wide groups of (mainly irritating) agents that may be considered low risk factors for (occupational) asthma.

Estimates of exposure to asthma causing agents were derived for each job held by study subjects and individual indices of exposure were created by integration over the whole occupational history of each case and control. Exposed individuals were defined taking into account 5 years of lag for high molecular weight exposures; for cases, exposures occurring in the last 5 years before the diagnosis were not considered, for controls, the lag was based on the interview date. We calculated the duration of occupational exposure using the total time of exposure among jobs excluding the 5 years previous to the date of diagnosis/interview. A five-year exposure lag was applied under the assumption that very recent exposures cannot be the causes of the lymphoma.

2.4. Statistical analysis

Unconditional logistic regression was used to assess the risk of lymphoma in relation to ever exposure to high molecular weight agents. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) for all lymphomas and lymphoma subtypes were