Immunoglobulin E Levels and Risk of Lymphoma in a Case-Control Study in Spain

Lis Ellison-Loschmann,[1,4] Yolanda Benavente,[1] Jeroen Douwes,[4] Enric Buendia,[2] Rebecca Font,[1] Tomás Álvaro,[5] Manolis Kogevinas,[3,6] and Silvia de Sanjosé[1]

[1]Epidemiology and Cancer Registry Unit, Institut Català d'Oncologia; [2]Immunology-Allergy Department, Hospital de Bellvitge; [3]Respiratory and Environmental Health Research Unit, IMIM, Barcelona, Spain; [4]Centre for Public Health Research, Massey University, Wellington, New Zealand; [5]Department of Pathology, Hospital Verge de la Cinta, Tortosa, Spain; and [6]University of Crete, Crete, Greece

Abstract

Epidemiologic studies have shown an inverse association between atopy and malignant lymphoma, but results are inconsistent. We investigated levels of IgE, before and after commencement of treatment, and evaluated lymphoma risk in relation to total and specific IgE levels. Serum levels of IgM, IgA, and IgG were also measured. We enrolled 467 newly diagnosed lymphoma cases and 544 hospital controls, matched for age, sex, and hospital. Lymphomas were histologically confirmed and categorized according to the WHO classification. Subjects provided blood for analysis of total and specific IgE levels, and total IgM, IgA, and IgG levels. Additional information was collected by interviewer-administered questionnaire. Controlling for age, sex, center, smoking status, and any treated asthma or eczema, we found that the overall risk of lymphoma was significantly lower in the high [odds ratio (OR), 0.39; 95% confidence interval (95% CI), 0.28-0.54] and middle (OR, 0.55; 95% CI, 0.40-0.74) tertiles for total serum IgE compared with the low tertile. Specific IgE to common aeroallergens (defined as ≥0.35 kU/L) was also inversely associated with risk of lymphoma (OR, 0.67; 95% CI, 0.45-1.00). Lymphoma was associated with IgA and IgM but not IgG. Mean levels of all immunoglobulins were decreased with more advanced malignancy, and total serum IgE levels were lower before treatment. The data suggest that the low levels of immunoglobulins seen in a wide range of lymphoma cases is likely to be linked to a lymphogenesis process rather than resulting from a selective protection due to an atopic process. Long-term cohort studies may be fundamental to fully evaluate these associations. (Cancer Epidemiol Biomarkers Prev 2007;16(7):1492–8)

Introduction

Results from epidemiologic studies of self-reported asthma and non–Hodgkin's lymphoma (NHL) have been inconsistent with various studies reporting an inverse association (1-5), no association (6), and in one study using cancer mortality data, a positive association (7). A recent large population-based case-control study involving 39,908 cases and 149,344 controls reported nonsignificant slightly reduced risks of NHL and chronic lymphocytic leukemia (CLL) and a statistically significant reduced risk of Hodgkin's lymphoma (HL) with asthma (8).

Only a few studies have used biological measures, most commonly skin prick tests or specific serum IgE, to assess the relationship between atopy and lymphoma risk. Melbye et al. (9) reported a significant inverse association with B-cell lymphoma and specific IgE reactivity with the strongest association seen with more advanced stage of disease. McCormick et al. (10) reported patients (n = 45) with CLL to have lower IgE levels than other patients with HL (n = 98), reticulum cell sarcoma (n = 33), and lymphosarcoma (n = 53). Several large cohort linkage studies have reported no association with cancer risk and atopy or allergy (11, 12). Elevated serum IgE levels have been reported in HL (13, 14) and advanced stage of HL disease has also been found to correlate with elevated IgE (15). Eosinophilia, a hallmark of atopy, is also frequently observed among HL patients (16). Finally, like a number of atopic conditions, some lymphomas such as NHLs have increased in incidence in recent decades in many parts of the developed world (17).

Although inconsistent, these studies suggest an etiologic link between lymphoma and atopy. The underlying mechanisms of the potential role of atopy in the risk of lymphoma are unclear. T cells are recognized as having a central role in the immune response to neoplasia as well as in the production and regulation of IgE (18). Both HL and NHL have been found to be associated with a T helper 2 dominant lymphocyte response (19, 20) similar to what has been shown in atopic subjects. Thus, lymphoma and atopy may, in part, develop in parallel, driven by the same underlying immunologic mechanisms, possibly due to the same etiologic factors such as improved hygienic conditions (21, 22). An alternative hypothesis is the antigenic stimulation hypothesis which proposes that immunostimulating exposures lead to an increased risk of atopy as well as malignancy caused by a mechanism in which chronic stimulation induced by the activated cells of the immune system result in a higher possibility of random mutations occurring in dividing cells (23). In contrast, the immune surveillance hypothesis proposes that allergic conditions may lead to a decreased risk of malignancy by enhancing the ability of the immune system to detect and eliminate malignant cells (24), which could explain the reported inverse associations between lymphoma and atopy. Elevated or reduced IgE levels may also be the result of the tumor itself rather than being representative of the ''true'' immune environment in which these cancers arose.

Using questionnaire information, the authors have previously shown that high molecular weight agents that stimulate the immune system through an IgE-mediated pathway were

Received 2/23/07; revised 4/17/07; accepted 4/20/07.

Grant support: An Erihapeti Rehu-Murchie Postdoctoral Research Fellowship (L. Ellison-Loschmann); a Programme Grant from the Health Research Council of New Zealand (Centre for Public Health Research); a Sir Charles Hercus Research Fellowship from the Health Research Council of New Zealand (J. Douwes); and partial funding from Marato TV3 (051530), FIS (04-0091), and CIBER (06/02/0073).

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Requests for reprints: Silvia de Sanjosé, Epidemiologia i Registre del Càncer, Institut Català d' Oncologia, Gran Via km 2.7, 08907 L' Hospitalet de Ll., Barcelona, Spain. Phone: 34-93-2607812; Fax: 34-93-2607787. E-mail: s.sanjose@iconcologia.net

doi:10.1158/1055-9965.EPI-07-0176

associated with an increased risk for young adult, nodular sclerosis HL, and a lowered risk for other B-cell lymphomas, especially diffuse large B-cell lymphoma (25). To explore this relationship further, we measured levels of IgE in blood in the same subjects and evaluated lymphoma risk in relation to total and specific IgE levels. Additionally, IgM, IgA, and IgG levels were also measured. Studies into these associations are of interest as it may reflect commonalities in etiology and could further clarify our understanding of the immunologic mechanisms underlying these diseases.

Materials and Methods

Subjects. The design of the Spanish lymphoma case-control study has been previously described and is part of the Epilymph multicenter collaboration (26). Briefly, cases were those who were newly diagnosed with a lymphoid neoplasm systematically recruited from three hospital centers in Spain (Barcelona, Tarragona, Madrid) during 1998 to 2004. A total of 700 cases were enrolled in the study. The diagnosis of lymphoma was verified by histology supplemented by immunochemistry test and flow cytometry. Cases were categorized according to the WHO Classification of Tumors of Haematopoietic and Lymphoid Tissue (26) and included all B-cell and T-cell neoplasms and HLs. All cases were tested for HIV infection status.

Controls (n = 655) were randomly selected patients admitted to the same hospitals as the cases during the same time period. Controls were frequency matched to cases by age, sex, and hospital, and selected from hospital admission lists.

Among cases, we excluded 26 subjects with (*a*) a serologic diagnosis of HIV or (*b*) a history of organ transplant. A further 207 cases did not have blood samples available for analysis. Among controls, 67 did not provide blood samples. Additionally, any patients hospitalized for organ transplant, systemic infection, or severe immunosuppression (n = 2) or whose primary reason for admission was due to an acute respiratory condition (n = 31) were also excluded. Thus, for the current analyses, the study comprised 467 cases (67% response rate) and 544 controls (83% response rate).

Data Collection. Information was collected via a structured face-to-face interview on demographic characteristics, medical and family history, and environmental exposures. Medical records were available to evaluate stage and treatment regimen for cases at entry to the study. Blood samples were collected from cases and controls at the time of interview with 259 cases providing their sample before the commencement of treatment. Written informed consent was obtained from all participants in accordance with the guidelines from each hospital center review board.

We had available information for two atopy related conditions that were determined by response to the question, ''Do you remember if you have suffered more than once from any of the following requiring medical treatment—asthma (yes/no) or eczema (yes/no)?''

Education level was categorized according to highest educational qualification attained and defined as ''high,'' university or tertiary institution; ''medium,'' high school qualification; and ''low,'' primary school level qualification. Information from the participants' work histories was used to assign four occupational class groupings based on the three-digit ISCO codes of their last held job (25): professionals (I), skilled manual and nonmanual (II), unskilled manual (III), and unclassified (IV; participants that had never had a job, were retired, students, or housewives).

Information on smoking history was obtained by questionnaire. For those who answered ''yes'' to the question ''Have you ever smoked regularly at least one cigarette/pipe a day for at least 6 months,'' additional questions were asked: age at starting smoking, type and number of cigarettes, and period of smoking for each type of cigarette. Participants were divided into categories of ''nonsmokers,'' ''ex-smokers,'' and ''current smokers'' based on the total information provided. Participants were also asked about alcohol intake and defined as ''regular drinkers'' if they reported consuming one alcoholic drink per day over a 6-month period.

Stage of disease was categorized as local or advanced using the combined information from three stage classification systems; the RAI classification used for staging of CLL, the MM classification for multiple myeloma, and the Ann Arbor staging classification for the remaining lymphoma categories.

Serum Collection. Ten milliliters of blood were collected in a citrate tube and the serum was obtained after centrifugation. The samples were stored in a freezer at −80°C until the analysis of specific and total IgE, IgM, IgA, and IgG in 2005 to 2006.

Total and Specific IgE Measures. Serum samples were analyzed for total IgE using immunometric assay by Immulite 2000 system (DPC). Total serum IgE ranged from 1 to 2,000 IU/mL for the whole study population. Complete data for analysis of total serum IgE was available for 1,060 subjects.

Measurement of serum specific IgE was carried out using the chemiluminescent immunoassay by Immulite 2000 system (DPC). The serum samples were analyzed for specific IgE in four panels that included 95% of the most common antigens in the study regions. Each panel contained five allergens: (*a*) grasses (*Dactylic glomerata, Festuca elatior, Lollium perenne, Phleum pretense, Poa pratensis*); (*b*) animals (*Dermatophagoides pteronyssinus*, cat, horse, dog, rabbit); (c) molds (*Penicillium notatum, Cladosporium herbarum, Aspergillus fumigatus, Candida albicans, Alternaria tenuis*); and (*d*) pollens (*Olea europaea, Platanus occidentalis, Cupressus sempervirens, Parietaria judaica, Plantago lanceolata*). Specific IgE positivity was defined as a positive test for specific IgE to at least one panel. Complete data for specific IgE analysis was available for 991 subjects for grasses, 1,001 subjects for animals, 1,003 subjects for molds, and 996 subjects for pollens.

IgA, IgG, and IgM Immunoglobulin Measures. Serum immunoglobulins were measured by nephelometry (BN II System, Dade Behring). Nine hundred ninety-five subjects had data available for measurements of IgA, IgG, and IgM.

Statistical Analyses. Immunoglobulin data for total serum values (IgE, IgA, IgG and IgM) were log transformed, resulting in a normal distribution of the data, and analyzed as continuous variables using geometric means and geometric SDs (GSD). Total serum IgE was then categorized into tertiles based on the IgE levels of the controls to define the following cut points: 1st tertile (reference category), 0.00 to 2.96 kU/L; 2nd tertile, 2.96 to 4.18 kU/L; and 3rd tertile, 4.18 to 7.61 kU/L. The reference values for the remaining immunoglobulins were as follows: IgA 88 to 410 mg/dL (males) and 74 to 370 mg/dL (females); IgG 690 to 1,400 mg/dL; and IgM 34 to 210 mg/dL (males) and 40 to 240 mg/dL (females). Specific IgE was analyzed as a categorical variable assigned as ''positive'' ≥0.35 kU/L or ''negative'' <0.35 kU/L. To evaluate associations between categorical variables and case-control status, the χ^2 test was used. Differences in continuous variables were evaluated by t test, using log-transformed values for immunoglobulin data.

Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) adjusted for age (analyzed as a continuous variable), sex, center, smoking [''never'' (reference group), ex-smoker, current] and any treated asthma or eczema (''no,'' a negative response for both conditions versus ''yes,'' a positive response for either

condition). The logistic regression analyses for lymphoma subgroups were done by comparing each lymphoma subgroup to all available controls. All analyses were conducted using STATA (STATA Statistical Software Release 9.0, 2004).

Results

Table 1 describes the characteristics of the study population. The mean age of controls was slightly younger (58 years) compared with that of cases (60.5 years). Cases were more likely to have been treated for asthma than controls but the opposite pattern was observed with treatment for eczema. Among controls, the geometric mean value of total serum IgE was 37.6 kU/L (GSD 4.5) compared with 18.4 kU/L (GSD 5.4) among cases. Total IgA ($P < 0.0001$) and IgM ($P = 0.003$) were also significantly higher in controls than in cases; however, no difference was seen with IgG. There was a significantly higher proportion of cases compared with controls (51.5% versus 32%, respectively) in the lowest total IgE tertile with the reverse observed in the highest tertile. Control subjects were more likely to have at least one positive specific IgE panel compared with cases. Controls were more often never smokers or current smokers compared with cases who were more likely to be

Table 1. Population characteristics for all subjects by case/control status

Individual variables	Controls, *n* (%)	Lymphoma cases, *n* (%)	*P*
Sex			
Male	279 (51.3)	258 (55.3)	
Female	265 (48.7)	209 (44.7)	0.21
Age (y), mean (SD)	58.0 (17.7)	60.5 (16.4)	0.02
Center			
Barcelona	456 (83.8)	371 (79.4)	
Madrid	49 (9.0)	50 (10.7)	
Tarragona	39 (7.2)	46 (9.9)	0.18
Education level			
Low	417 (76.7)	352 (75.4)	
Medium	89 (16.4)	71 (15.2)	
High	38 (7.0)	44 (9.4)	0.35
Smoking history			
Never	260 (48.0)	219 (47.2)	
Ex-smoker	144 (26.6)	155 (33.4)	
Current	138 (25.5)	90 (19.4)	0.02
Alcohol consumption			
Regular drinker	259 (47.7)	208 (44.8)	
Nonregular drinker	284 (52.3)	256 (55.2)	0.36
Social class*			
I	12 (2.2)	19 (4.1)	
II-III	74 (13.6)	74 (15.9)	
IV-V	298 (54.9)	257 (55.2)	
Unclassified	159 (29.3)	116 (25.0)	0.14
No. siblings			
Only child	24 (4.4)	23 (4.9)	
1 sibling	88 (16.2)	83 (17.8)	
2-3 siblings	209 (38.5)	160 (34.3)	
>3 siblings	223 (40.9)	201 (43.0)	0.58
Atopy-related conditions			
Treated for asthma	49 (9.1)	40 (8.6)	0.81
Treated for eczema	44 (8.1)	60 (12.9)	0.01
Any asthma or eczema	89 (16.3)	94 (20.2)	0.11
Immunoglobulin measures			
Total IgE, mean (GSD) †	37.6 (4.5)	18.4 (5.4)	<0.0001 ‡
Tertile 1 (0.00-2.96 kU/L)§	177 (33.0)	240 (51.5)	
Tertile 2 (2.96-4.18 kU/L)§	179 (33.3)	129 (27.7)	
Tertile 3 (4.18-7.61 kU/L)§	181 (33.7)	97 (20.8)	<0.0001 ‡
Specific IgE			
Positive specific IgE for ≥1 panels‖	81 (15.5)	50 (11.0)	0.04
Positive specific IgE for ≥2 panels‖	15 (3.3)	12 (2.9)	0.73
Total IgA, mean (GSD) †	224.8 (1.7)	156.6 (2.4)	<0.0001 ‡
Total IgM, mean (GSD) †	96.06 (1.8)	79.76 (2.7)	0.003 ‡
Total IgG, mean (GSD) †	822.80 (1.4)	843.64 (1.8)	0.41 ‡
Lymphoma type			
All lymphoma¶	544 (53.8)	467 (46.2)	
NHL**		247 (45.2)	
B cell ††		384 (77.0)	
T-cell		35 (7.5)	
HL		48 (10.4)	

*Social class was defined as follows: I, managers and professionals; II to III; technicians and allied professionals, other nonmanual; IV to V, skilled manual, semiskilled/unskilled manual, IV, unclassified.

†Geometric mean value with GSD using log-transformed data.

‡*t* test mean of ln value.

§Tertiles were calculated using log-transformed total IgE values.

‖Positive panel for either grass, animals, molds, or pollens with positive specific IgE defined as ≥0.35 kU/L.

¶All lymphoma category includes B-cell lymphomas: CLL, lymphoplasmatic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma (MM), marginal zone B-cell lymphoma, follicular lymphoma, diffuse large-cell lymphoma, other B-cell lymphoma; T-cell lymphomas: mycosis fungoides/Sézary, other T-cell lymphoma; HL.

**NHL category excludes CLL, MM, and HL.

††B-cell lymphoma category excludes T-cell lymphoma and HL.

ex-smokers. Mean values for total serum IgE were significantly different between cases and controls for all categories of smoking ($P < 0.000$; data not shown). Mean total IgE was lower in cases compared with controls independent of the atopic related condition (either asthma or eczema; data not shown).

Controlling for age, sex, center, smoking status, and any treated asthma or eczema, we found the overall risk of lymphoma to be significantly lower in the high (OR, 0.39; 95% CI, 0.28-0.54) and middle (OR, 0.55; 95% CI, 0.40-0.74) tertiles for total serum IgE compared with the low tertile (Table 2). There was a general pattern of reduced risk of B-cell lymphoma with increasing total serum IgE. A significant association was observed for NHL (OR, 0.54; 95% CI, 0.36-0.81) and B-cell category (OR, 0.34; 95% CI, 0.23-0.48) and for the subcategories of CLL, MM, and follicular lymphoma in the low compared with the high tertiles of total IgE. Both HL and T-cell lymphoma categories showed a decreased risk with medium and high levels of total IgE but none of the associations were statistically significant (Table 2).

The associations between positive specific IgE and lymphoma for all cases and for those cases with blood taken before commencement of treatment are presented in Table 3. Eleven percent of all lymphoma cases had a positive specific IgE test compared with 15.6% of controls. The adjusted OR for all lymphoma was 0.67 (95% CI, 0.45-1.00) and there was a borderline significant effect seen for B-cell lymphoma (OR, 0.66; 95% CI, 0.43-1.03). There was little modification to the associations in the analysis of those in the before treatment group. All of multivariate estimates were below 1.0; however, none of the associations reached statistical significance.

Table 4 presents mean values for all immunoglobulin classes by stage of disease and timing of extraction of blood sample (either before or after commencement of treatment) among cases. The mean IgE level was greater ($P = 0.01$) in cases with blood samples taken posttreatment (26.4 kU/L, GSD 6.19) than in those with blood samples taken before treatment (15.5 kU/L, GSD 4.87). No significant differences were observed for the other immunoglobulins by blood status. Advanced stage of disease was associated with lower mean values for all immunoglobulin classes, IgE ($P = 0.06$). The geometric mean value of IgE was 16.2 kU/L (GSD 5.41) for advanced compared with 21.6 kU/L (GSD 5.20) for localized disease. Similarly, lower mean values was seen in all other immunoglobulin classes, IgA ($P = 0.001$), IgG ($P = 0.001$), and IgM ($P = 0.37$), with advanced compared with localized stage of disease.

Discussion

We found that the overall risk of lymphoma was significantly lower in subjects with high total serum IgE. This association was observed for NHL and B-cell lymphoma overall, and for the individual B-cell categories of CLL, MM, and follicular lymphoma. These findings were independent of age, sex, center, smoking status, and any history of treated asthma or eczema. They depended, however, on the extent of disease with the strongest effect observed for cases with a more advanced stage. Positive specific IgE was also inversely associated with lymphoma overall.

Our results are consistent with several previous studies that showed an inverse association between atopy and lymphoma (9, 10). In particular, a recent case-control study conducted in Finland (9) reported an inverse risk association between overall NHL and positive specific IgE (OR, 0.68; 95% CI, 0.58-0.80) with risk associations for some (CLL, follicular, and lymphoplasmacytic) but not all (diffuse, marginal zone, and T cell) individual NHL subtypes being similar to those reported in the current study. On the other hand, some studies have shown no, or even an opposite, association (11, 27).

We previously reported a decreased risk of B-cell lymphoma (OR, 0.75; 95% CI, 0.50-1.12) to be associated with occupational exposure to high molecular weight agents known to stimulate the immune system through an IgE-mediated pathway whereas for HL, there was an increased risk, particularly of nodular sclerosis (OR, 3.22; 95% CI, 1.14-9.09; ref. 25). The current analyses support the earlier results in relation to B-cell lymphoma, but not HL, where we found a protective effect for both total and specific serum IgE. The majority of previous studies have reported an increased risk of HL with elevated IgE levels (15, 16). Nonetheless, a recent large case-control study, using data from population based registries, reported asthma to be associated with a significantly decreased risk of HL (OR, 0.6; 95% CI, 0.4-0.9; based on 18 exposed cases), which is in accordance with our current results; after an induction

Table 2. Multivariate analysis of lymphoma and total serum IgE

	Total population, *N* (%)	1st tertile (0.00-2.96 kU/L)*		2nd tertile (2.96-4.18 kU/L)*		3rd tertile (4.18-7.61 kU/L)*	
		n (%)		*N* (%)	OR (95% CI)	*N* (%)	OR (95% CI)
Control	537 (53.5)	177 (32.0)		179 (33.3)		181 (33.7)	
All lymphomas	466 (46.5)	240 (51.5)	Reference	127 (27.7)	0.55 (0.40-0.74)	97 (20.8)	0.39 (0.28-0.54)
Lymphoma subgroups							
NHL †	246 (53.0)	108 (43.9)	Reference	77 (31.3)	0.72 (0.49-1.03)	61 (24.8)	0.54 (0.36-0.81)
B cell	384 (82.4)	209 (54.4)	Reference	109 (28.4)	0.54 (0.40-0.75)	66 (17.2)	0.34 (0.23-0.48)
CLL	104 (22.3)	72 (69.2)	Reference	25 (24.0)	0.34 (0.20-0.57)	7 (6.7)	0.10 (0.04-0.22)
Lymphoplasmatic lymphoma	19 (4.1)	11 (57.9)	Reference	3 (15.8)	0.28 (0.07-1.06)	5 (26.3)	0.48 (0.15-1.49)
Splenic marginal zone	23 (4.9)	12 (52.2)	Reference	6 (26.1)	0.55 (0.19-1.59)	5 (21.7)	0.47 (0.15-1.46)
Plasma cell myeloma	68 (14.6)	44 (64.7)	Reference	15 (22.1)	0.38 (0.20-0.71)	9 (13.2)	0.24 (0.11-0.53)
Marginal zone B cell	23 (4.9)	9 (39.1)	Reference	7 (30.4)	0.93 (0.32-2.67)	7 (30.4)	0.93 (0.31-2.78)
Follicular lymphoma	36 (7.7)	19 (52.8)	Reference	13 (36.1)	0.67 (0.31-1.47)	4 (11.1)	0.18 (0.06-0.56)
Diffuse large-cell lymphoma	79 (16.9)	32 (40.5)	Reference	29 (36.7)	0.94 (0.53-1.65)	18 (22.8)	0.60 (0.31-1.15)
Other B-cell lymphoma	32 (6.9)	10 (31.3)	Reference	11 (34.4)	0.95 (0.38-2.37)	11 (34.4)	0.97 (0.38-2.47)
HL	48 (10.3)	16 (33.3)	Reference	12 (25.0)	0.57 (0.25-1.31)	20 (41.7)	0.72 (0.33-1.54)
T-cell lymphoma	34 (7.3)	15 (44.1)	Reference	8 (23.5)	0.47 (0.19-1.17)	11 (32.4)	0.49 (0.20-1.20)
Mycosis fungoides/Sézary	16 (3.4)	7 (43.8)	Reference	4 (25.0)	0.51 (0.14-1.89)	5 (31.3)	0.43 (0.11-1.65)
Other T cell	18 (3.9)	8 (44.4)	Reference	4 (22.2)	0.47 (0.13-1.63)	6 (33.3)	0.54 (0.16-1.79)

NOTE: Adjusted for age, sex, center, smoking status, any treated asthma or eczema.
*Tertiles were defined as follows: 1st tertile (reference category), 0.00 to 2.96 kU/L; 2nd tertile, 2.96 to 4.18 kU/L; 3rd tertile, 4.18 to 7.61 kU/L (using log-transformed total IgE data).
†NHL category excludes CLL, MM, and HL.

Table 3. Mulitvariate analysis of lymphoma and specific IgE (≥0.35 kU/L) for all cases and for all cases before treatment group

	All cases			Before treatment group		
	N	*n* (%)	OR* (95% CI)	*N*	*n* (%)	OR* (95% CI)
Controls	524	82 (15.6)	Reference	524	82 (15.6)	Reference
All lymphoma	456	50 (11.0)	0.67 (0.45-1.00)	246	25 (10.2)	0.66 (0.40-1.10)
Lymphoma subgroups						
NHL †	239	31 (13.0)	0.78 (0.49-1.25)	111	12 (10.8)	0.64 (0.32-1.27)
B cell	375	36 (9.6)	0.66 (0.43-1.03)	215	19 (8.8)	0.68 (0.45-1.03)
CLL	102	4 (3.9)	0.30 (0.10-0.86)	85	4 (4.7)	0.62 (0.38-1.04)
Lymphoplasmatic lymphoma	18	1 (5.6)	0.42 (0.05-3.35)	12	0 (0.0)	0.68 (0.41-1.13)
Splenic marginal zone	23	0 (0.0)	0.75 (0.23-2.47)	19	0 (0.0)	0.65 (0.39-1.07)
Plasma cell myeloma	67	5 (7.5)	0.57 (0.21-1.50)	34	4 (11.8)	0.62 (0.38-1.02)
Marginal zone B cell	21	5 (23.8)	1.81 (0.60-5.42)	8	1 (12.5)	0.73 (0.45-1.19)
Follicular lymphoma	34	4 (11.8)	0.64 (0.21-1.98)	11	1 (9.1)	0.67 (0.41-1.09)
Diffuse large-cell lymphoma	78	13 (16.7)	1.12 (0.57-2.20)	30	7 (23.3)	0.71 (0.44-1.12)
Other B-cell lymphoma	32	4 (12.5)	0.65 (0.21-2.04)	16	2 (12.5)	0.65 (0.39-1.06)
HL	48	10 (20.8)	0.69 (0.30-1.56)	16	5 (31.3)	0.64 (0.40-1.03)
T-cell lymphoma	33	4 (12.1)	0.52 (0.15-1.85)	15	1 (11.1)	0.68 (0.42-1.11)
Mycosis fungoides/Sézary	16	2 (12.5)	0.33 (0.04-2.85)	6	0 (0.0)	0.66 (0.40-1.08)
Other T cell	17	2 (11.8)	0.82 (0.17-3.94)	9	1 (11.1)	0.67 (0.41-1.11)

*Adjusted for age, sex, center, smoking status, any treated asthma or eczema.
†NHL category excludes CLL, MM, and HL.

period of 10 years after first asthma diagnosis, the OR was still below unity (OR, 0.7), but the result was no longer statistically significant (8).

It has been postulated that the association between HL and high serum IgE levels is linked to suppressor lymphocyte dysfunction ($CD8^+$) and is distinct from the increase in allergen-specific IgE, which is associated with atopy (28); however, it is unclear why very high levels of total IgE and a marked presence of eosinophilia are found in only some patients with HL and not others (16, 29). Eosinophils are a source of numerous cytokines and growth factors and seem to have a role in both pro- and anti-inflammatory activities as well as immunoregulatory ones (30). Thus, it would seem plausible that the association between atopy and lymphoma risk could be dependent on the particular allergic condition, atopic sensitization, and the histologic type of lymphoma, as has been suggested from previous studies on atopy and other cancer types (31-33), and, if so, this may explain some of the variance in results from previous studies of lymphoma risk and atopy.

An absence of microbial challenge in early life, referred to as the ''hygiene hypothesis,'' has been implicated in the increased prevalence of atopy (34) and allergic asthma (35) seen primarily in developed countries over the last three decades. Various factors associated with exposure to infection in early life have also been found to be associated with a reduced lymphoma risk, including early birth order (2) and contact with some farm animals (21), although the results are not consistent across studies (21). A recent European multicenter study found an elevated lymphoma risk for having one or more younger siblings, whereas having one or more older siblings was associated with a decreased risk of lymphoma (36). Among the control population in the current study, we assessed IgE levels and a number of factors relating to the hygiene hypothesis, including being a firstborn child, number of siblings, sharing a bedroom, and sharing a bed as a child (data not shown). We found a difference in IgE levels for bed sharing as a child ($P = 0.05$) but not for any of the other variables examined. Other explanations for the potential link between atopy and lymphoma include the two contradictory hypotheses raised in the introduction; that is, the antigenic stimulation hypothesis (23) and the immune surveillance hypothesis (24), with the latter supporting our findings of a protective effect of atopy.

There is a puzzling aspect to our results, however, which argues against a definitive conclusion supporting the immune surveillance hypothesis. Our finding of an inverse association with elevated total IgE and positive specific IgE (in the pretreatment group) was seen for every histologic subgroup of lymphoma. Lymphomas comprise a diverse group of neoplasms whose behaviors range from indolent to very aggressive and the fact that our results were uniform across such a wide range of known separate pathologic entities would favor the explanation that a generalized immune response resulting in depression of IgE levels occurs early on following the development of a malignant lymphoma.

Although use of a biological marker such as immunoglobulins may reduce some of the misclassification bias associated with questionnaire data, interpretation of the data is not straightforward. In particular, lymphoma is an immune cancer

Table 4. Mean values for all immunoglobulins among lymphoma cases by blood status and stage of disease

Variables	IgE*				IgA*				IgM*				IgG*			
	n	Mean	GSD	*P* †	*n*	Mean	GSD	*P* †	*n*	Mean	GSD	*P* †	*n*	Mean	GSD	*P* †
Blood																
Before treatment	253	15.5	4.87		247	152.7	2.63		247	81.9	2.75		247	878.5	1.75	
After treatment	75	26.4	6.19	0.01	75	174.3	2.47	0.23	75	82.2	2.71	0.98	75	947.0	1.90	0.33
Stage of disease																
Localized	212	21.6	5.20		210	180.6	2.04		210	83.3	2.12		210	948.4	1.60	
Advanced	248	16.2	5.41	0.06	244	137.8	2.66	0.001	244	76.7	3.20	0.37	244	764.7	1.91	0.001

*Geometric mean value with GSD using log-transformed data.
†*t* test mean of ln value.

and thus, may directly affect immunoglobulin production (e.g., through immunosuppression); thus, IgE, IgA, IgG, and IgM levels may not accurately reflect the immune environment in which the lymphoma developed. Related to this is the fact that stage of disease needs to be taken into account as the progression of malignancy is generally associated with suppression of immunoglobulin production (37), although elevated levels of IgA and IgG with advanced stage of disease have been reported in studies of cutaneous T-cell lymphoma (38). Furthermore, cancer treatment regimens are extremely immunosuppressive and may thus have an effect on biomarker levels (14). To assess whether these issues played a role in our findings, we compared immunoglobulin levels between pretreated and posttreated cases, and between cases with localized and advanced stage of diseases. Immunoglobulin levels were lower in those with a more advanced stage of disease, similar to findings reported by others (29, 37, 39); we also found lower immunoglobulin levels in pretreated cases. The difference was greatest for IgE between pretreatment and posttreatment groups, and for IgE, IgA, and IgG by localized versus advanced stage of disease. The differences in IgA, IgM, and IgG, although not statistically significant, were consistent with the IgE results that could indicate that the inverse association with IgE may be due to the process of lymphogenesis. However, the percentage concordance between self-reported asthma and total IgE levels (data not shown) were not markedly different between cases and controls (16% versus 10%, respectively), suggesting that lymphoma-induced IgE suppression was not a likely explanation for the case/control differences in IgE observed in the current analyses. One other study (9) has reported a stronger inverse association between NHL and positive specific IgE with more advanced stage of disease. The same study also showed no difference in IgE levels in cases and controls using serum collected during pregnancy years before an NHL diagnosis. The authors concluded that the association between atopy and NHL was therefore most likely explained by reverse causality, with the development of NHL suppressing the immunologic response to allergens. However, it is also possible that these observations could have been affected by altered levels of IgE, which have been documented to occur during pregnancy, particularly in allergic women (40, 41).

Mean levels of total IgE, IgA, and IgM were higher in controls compared with cases in the current study (Table 1). IgM is usually the first immunoglobulin to be produced in a general immune response; thus, high levels of IgM in our control population may be due to the condition that subjects were hospitalized for; however, we had no additional information to explore this further. IgA is the principal secretory immunoglobulin and is found in the mucosal linings of the mouth, gastrointestinal, and respiratory tract. The role of IgA in the etiology of allergic disease such as asthma is unclear. Both IgA and IgE are found on the surface of eosinophils and an increased expression of IgA receptors have been found on eosinophils of allergic individuals (42). IgA has also been implicated as a contributor to allergic inflammation in asthmatic airways (42). Thus, it may be that our result of both lowered serum IgA and IgE among lymphoma cases is consistent with these immunoglobulins having a role in the promotion of allergic disease. In addition, IgE levels were clearly lower among B-cell lymphomas subtypes compared with other lymphoma types, suggesting an IgE/atopy pathogenic mechanism common to B-cell lymphomas.

Our participation rates for the study were relatively high with 67% in cases and 83% in controls limiting the potential of selection bias particularly because the main reason for nonparticipation was due to lack of available serum. It is possible that the use of hospital controls may have biased our estimates. We were careful to exclude control patients who had been admitted for any acute respiratory condition, including asthma, resulting in a prevalence of asthma in the control population (9%), which was similar to that reported in a recent population study (43) indicating that selection bias on the basis of asthma was minimal. However, as mentioned previously, a potential bias might arise from depression of IgE by the lymphoma or as a result of treatment. IgE levels have previously been reported to be associated with smoking (44), myeloma (45), and human immune deficiency virus (46). In the current study, we excluded any subjects with possible immune deficiency disorders and adjusted for a number of potential confounding factors in our initial analyses, of which only smoking and having been treated for an atopy-related condition were found to be significant, and, thus, were included in our final models.

In conclusion, we found that the overall risk of lymphoma was significantly lower, particularly among B-cell lymphoma subtypes, in subjects with high total serum IgE. The data presented, however, suggests that the low levels of immunoglobulins seen in a wide range of lymphoma cases is likely to be linked to a lymphogenesis process rather than a process of selective protection conferred by atopic disease. Several epidemiologic studies have associated atopy and allergic processes with a lower lymphoma risk and the mechanisms of such a development are yet to be understood. Long-term cohort studies may be fundamental to fully evaluate these associations.

Acknowledgments

We thank Neil Pearce and Wendy Cozen for valuable comments on earlier drafts of this article.

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Lis Ellison-Loschmann, Yolanda Benavente, Jeroen Douwes, et al.

Cancer Epidemiol Biomarkers Prev 2007;16:1492-1498.