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# Prediagnostic immunoglobulin E levels and risk of chronic lymphocytic leukemia, other lymphomas and multiple myeloma-results of the European Prospective Investigation into Cancer and Nutrition

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**Previous epidemiological studies suggest an inverse association between allergies, marked by elevated immunoglobulin (Ig) E levels, and non-Hodgkin lymphoma (NHL) risk. The evidence, however, is inconsistent and prospective data are sparse. We examined the association between prediagnostic total (low: <20; intermediate: 20–100; high >100 kU/l) and specific IgE (negative: <0.35; positive ≥0.35 kU/l) concentrations against inhalant antigens and lymphoma risk in a study nested within the European Prospective Investigation into Cancer and Nutrition cohort. A total of 1021 incident cases and matched controls of NHL, multiple myeloma (MM) and Hodgkin lymphoma with a mean follow-up time of 7 years were investigated. Multivariate-adjusted odds ratios (ORs) with 95% confidence intervals (CI) were calculated by conditional logistic regression. Specific IgE was not associated with the risk of MM, B-cell NHL and B-cell NHL subtypes. In contrast, total IgE levels were inversely associated with the risk of MM [high level: OR = 0.40 (95% CI = 0.21–0.79)] and B-cell NHL [intermediate level: OR = 0.68 (95% CI = 0.53–0.88); high level: OR = 0.62 (95% CI = 0.44–0.86)], largely on the basis of a strong inverse association with chronic lymphocytic leukemia [CLL; intermediate level: OR = 0.49 (95% CI = 0.30–0.80); high level: OR = 0.13 (95% CI = 0.05–0.35)] risk. The inverse relationship for CLL remained significant for those diagnosed 5 years after baseline. The findings of this large prospective study demonstrated significantly lower prediagnostic total IgE levels among CLL and MM cases compared with matched controls. This corresponds to the clinical immunodeficiency state often observed in CLL patients prior to diagnosis. No support for an inverse association between prediagnostic levels of specific IgE and NHL risk was found.**

## Introduction

Lymphomas constitute a heterogeneous group of malignancies involving lymphocytes. They represent the fifth most common cause of cancer incidence among women and the sixth among men (1). Epidemiologic observations point to important associations between lymphoma development and deregulation of immune responses (2). For non-Hodgkin lymphomas (NHLs) and less so for Hodgkin lymphoma, strongly increased risks have been observed among immunosuppressed organ transplant recipients and certain autoimmune diseases were associated with lymphoma risk (3,4). In contrast, epidemiologic data, especially from case-control studies, suggest a possible inverse relationship between the risk of NHL and atopic conditions, such as hay fever, allergic asthma and allergic reactions against high-molecular-weight allergens in occupational exposure settings (2,5,6). Atopic conditions, including those against occupational allergens (7), are caused by hypersensitivity to environmental allergens and are characterized by an immune response shifted towards an increased type 2 (relative to type-1) T-helper cell activity and increased immunoglobulin (Ig) E production (8,9). It has been speculated that this type of increased immune response could be linked to stronger immune surveillance and host defense against malignant disease ('immune surveillance hypothesis') (10).

These observations have led to speculations that a relatively large proportion of NHL occurrences could be related to comparatively minor, and potentially subclinical, variations in immune function (2).

**Abbreviations:** CI, confidence interval; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; EPIC, European Prospective Investigation into Cancer and Nutrition; FL, follicular lymphoma; ICD-O-2, International Classification of Diseases for Oncology; Ig, immunoglobulin; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; OR, odds ratio.

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However, considerable debate still exists as to whether the association of NHL with atopic conditions and related variations in immune response reflect a cause or an effect of lymphoma development (11–13). To date, only a few prospective studies have assessed specific and/or total IgE levels in relation to subsequent lymphoma diagnosis (12,14,15). Two Swedish cohorts, which measured individuals for total IgE, found no association with either the risk of cancer in general or with lymphoma (14,15). In a Finnish cohort of pregnant women, no association between NHL and specific IgE reactivity was found, except in women who developed NHL <5 years after the blood samples were drawn, again suggesting that reduced antibody levels could be a consequence rather than a cause of NHL development (12). Finally, in several cohort studies, contrary to many case-control studies, no protective effect was found (3,14,16–21), and some studies even observed an increase in lymphoma risk in association with a self-reported history of allergies (3,16,18,20,21).

To further clarify the prospective relationship between atopy-related immune response and the risk of lymphoma and its main subtypes, we measured plasma levels of total IgE and specific IgE against inhalant allergens in 1021 incident cases of lymphoma and 1021 matched controls, within the European Prospective Investigation into Cancer and Nutrition (EPIC).

## Materials and methods

EPIC is a large prospective cohort study with over 500 000 participants enrolled from 23 centers in Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom (22). In most EPIC study centers, study participants were recruited from the general population of the local geographical areas. Exceptions were the Utrecht subcohort in the Netherlands and the Florence subcohort in Italy, where participants were recruited among women participating in a population-based breast cancer screening program, and the French subcohort, which was based on women who were members of the health insurance system or state-school employees. In addition, the five Spanish subcohorts, and the Turin and Ragusa subcohorts in Italy included high proportions (46–100%) of blood donors. Between 1992 and 1998, standardized lifestyle and personal history questionnaires were collected from all study participants, and for over 430 000 participants, a blood sample was also collected at first recruitment. Blood samples were stored in a central bio-repository at the International Agency for Research on Cancer (Lyon, France, −196°C in liquid nitrogen) for all countries except Denmark (−150°C in nitrogen vapor) and Sweden (in −80°C freezer). All participants gave written informed consent to participate in the study. The research was approved by the local ethics committees in the participating countries and by the internal review board of the International Agency for Research on Cancer (Lyon, France).

### *Follow-up for cancer incidence and vital status*

Data on vital status in EPIC are collected through record linkage with regional and/or national mortality registries, except in Germany and Greece, where data are collected through active follow-up and checks through municipal population registries. Cancer incidence is determined through record linkage with regional cancer registries (Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom; complete, for the present report, up to December 2004) or via a combination of methods, including the use of health insurance records, contacts with pathology registries, and active follow-up through participants and their next of kin (France, Germany and Greece complete up to December 2006). Cases with lymphoid cancers were originally classified according to the Second revision of the International Classification of Diseases for Oncology (ICD-O-2), but were subsequently reclassified according to the WHO classification of hematopoietic and lymphoid tissue cancers, third edition (23), using a program available on the United States National Cancer Institute Surveillance, Epidemiology and End Results website (http://seer.cancer.gov/) and the expertise of pathologists. If the ICD-O-2 codes could not be exactly translated to ICD-O-3, a patient was categorized as 'lymphoma, not otherwise specified'. Participants of the French cohort ($n$ = 24 371) with available blood samples) were excluded from the study because of incomplete coding for lymphoid neoplasms, when the present project was started. From the remaining individuals, we excluded cases who had any form of cancer at time of blood draw except benign skin tumors ($n$ = 27 083). The final analyses included 1031 lymphoma cases available for matching.

### *Nested case-control design and participant selection*

For each lymphoma case, one control was selected by incidence density sampling from a total of 360 762 eligible controls available, who were alive and without a cancer diagnosis cancer at the time a corresponding index case with lymphoma had been diagnosed. Matching criteria were study centre, sex, blood donor status, age at blood collection (±12 months at blood collection), date (±3 months) and time of blood collection. Following further exclusion of individuals with missing measurements, data from 2042 subjects (1021 matched case-control pairs) were available for analysis. Cases included Hodgkin lymphoma ($n$ = 54), B-cell NHL ($n$ = 634), T-cell NHL ($n$ = 36), multiple myeloma (MM; $n$ = 226) and lymphoma not otherwise specified ($n$ = 71; collectively referred as NOS). The B-NHL subtypes included diffuse large B-cell lymphoma (DLBCL; $n$ = 132), follicular lymphoma (FL; $n$ = 116) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma ($n$ = 187). Due to their limited sample size, Hodgkin lymphoma and T-cell NHL were not considered in the analysis.

### *Laboratory analysis*

Circulating plasma total and specific IgE antibody concentration were determined by an automated fluorescence enzyme immunoassay with the ImmunoCAP 100 (Thermo Fisher Scientific, Phadia, GmbH, Freiburg, Germany). The following specific IgE antibodies against the eight most common allergens (with their international allergen codes) were quantified: g6-timothy grass, g12-cultivated rye, t3-common silver birch, w6-mugwort, d1-*Dermatophagoides pteronyssinus*, e1-cats epithelium and dander, e5-dog dander and m2-*Cladosporium herbarum*. Analyses were performed in the Division of Cancer Epidemiology of the German Cancer Research Center in Heidelberg. Laboratory personnel were blinded to the case or control status of participants. Plasma samples from each case-control set were assayed within the same analytical batch. About 40 µl of plasma was required for each assay. Two plasma quality control samples were analyzed within each batch. The intra-assay coefficients of variation were 7.0% (at 3.60 kU/l) and 6.7% (at 152.5 kU/l) for total IgE and 14.2% (at 0.08 kU/l) and 5.6% (at 66.2 kU/l) for specific IgE. The interassay coefficients of variation were 15.2% (at 3.60 kU/l) and 11.9% (at 145.3 kU/l) for total IgE and 15.7% (at 0.08 kU/l) and 8.8% (at 57.4 kU/l) for specific IgE.

### *Statistical analysis*

Differences between cases and controls in IgE levels and continuous baseline covariates were tested by paired $t$-tests for each case-control set. Group differences in geometric mean IgE levels by baseline covariates were identified using pairwise $t$-tests and analysis of variance. For all further analyses, total IgE was categorized into three levels: reference (<20 kU/l; probability of allergic symptoms low), intermediate (20–100 kU/l; probability of allergic symptoms moderate) and high (>100 kU/l; probability of allergic symptoms high) (24). Likewise, specific IgE was categorized into 'negative' (<0.35 kU/l) and 'positive' (≥0.35 kU/l) (25), and in additional analyses was further categorized into a 'negative' reference category (<0.35 kU/l) and tertiles for positive values (≥0.35 kU/l) based on the distribution of IgE levels in the controls (first tertile, 0.35–1.06 kU/l; second tertile, 1.07–4.33 kU/l; third tertile ≥4.33 kU/l). Conditional logistic regression, stratified by the case-control set, was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) of lymphoma risk in relation to total and specific IgE levels. Statistical adjustments were made for smoking status (categorical: life-long non-smoker, current smoker, ex-smoker), alcohol consumption at the time of recruitment (g/d), highest school level [categorical: none, primary school completed, technical/professional school, secondary school, longer education (including university degree)].Test for linear trend was conducted by assigning ordinal scores (1–3) to each of the categories and treating the variable as continuous in the regression model. Missing value categories were added to the various confounding variables in order to retain all of the observations in the analysis (Table I). All analyses were also performed after the exclusion of the individuals with missing values in any of the variables ($n$ = 189). The results obtained from the two approaches did not differ meaningfully. Stratified analysis by time to diagnosis (<2/≥2; <3/≥3; <5/≥5 years after baseline) were conducted to evaluate the influence of time on the investigated associations. The likelihood ratio $\chi^2$ test was used to assess heterogeneity in the association between total and specific IgE levels and all main variables. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). All tests of statistical significance were two-sided, and $P$-values <0.05 were considered significant.

## Results

In total, 1021 incident lymphoma cases and 1021 controls were enrolled in this study. Lymphoma cases were on average 56 years old (range: 29–78 years) and had a mean follow-up time of 7.0 years (range: 2 days to 13.7 years). Overall, lymphoma cases and controls showed no differences in level of formal education, smoking status,



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**Table I.** Distribution and geometric mean of prediagnostic specific and total IgE levels

| | Specific IgE (kU/l) | | | | | | Total IgE (kU/l) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Controls ($n$ = 1021) | | | Cases ($n$ = 1021) | | | Controls ($n$ = 1021) | | | Cases ($n$ = 1021) | | |
| | $N$ (%) | Mean | $P^a$ | $N$ (%) | Mean | $P$ | $N$ (%) | Mean | $P$ | $N$ (%) | Mean | $P$ |
| Sex | | | | | | | | | | | | |
| Male | 526 (52) | 0.20 | <0.001 | 526 (52) | 0.19 | 0.002 | 526 (52) | 39.28 | <0.001 | 526 (52) | 26.75 | <0.001 |
| Female | 495 (48) | 0.15 | | 495 (48) | 0.14 | | 495 (48) | 22.48 | | 495 (48) | 18.10 | |
| Age at recruitment | | | | | | | | | | | | |
| <40 | 31 (3) | 0.32 | 0.042 | 31 (3) | 0.26 | 0.006 | 31 (3) | 28.36 | 0.926 | 31 (3) | 36.10 | 0.003 |
| 40–49 | 141 (14) | 0.21 | | 147 (14) | 0.22 | | 141 (14) | 32.20 | | 147 (14) | 31.89 | |
| 50–59 | 455 (45) | 0.17 | | 451 (44) | 0.17 | | 455 (45) | 29.59 | | 451 (44) | 21.83 | |
| ≥60 | 394 (39) | 0.16 | | 392 (38) | 0.14 | | 394 (39) | 29.76 | | 392 (38) | 18.86 | |
| Season of blood donation | | | | | | | | | | | | |
| Spring | 294 (29) | 0.16 | 0.454 | 297 (29) | 0.16 | 0.872 | 294 (29) | 27.90 | 0.643 | 297 (29) | 22.42 | 0.782 |
| Summer | 181 (18) | 0.17 | | 183 (18) | 0.18 | | 181 (18) | 30.43 | | 183 (18) | 24.53 | |
| Autumn | 303 (30) | 0.19 | | 299 (29) | 0.16 | | 303 (30) | 32.27 | | 299 (29) | 21.29 | |
| Winter | 243 (24) | 0.18 | | 242 (24) | 0.16 | | 243 (24) | 29.44 | | 242 (24) | 21.14 | |
| Smoking history | | | | | | | | | | | | |
| Life-long non-smoker | 440 (43) | 0.17 | 0.020 | 422 (41) | 0.16 | 0.928 | 440 (43) | 23.45 | <0.001 | 422 (41) | 18.27 | <0.001 |
| Current smoker | 202 (20) | 0.20 | | 190 (19) | 0.17 | | 202 (20) | 42.66 | | 190 (19) | 31.88 | |
| Ex-smoker | 309 (30) | 0.16 | | 336 (33) | 0.17 | | 309 (30) | 30.92 | | 336 (33) | 21.84 | |
| Missing information | 70 (7) | 0.26 | | 73 (7) | 0.15 | | 70 (7) | 44.00 | | 73 (7) | 27.52 | |
| Alcohol at recruitment | | | | | | | | | | | | |
| 0 g/day | 111 (11) | 0.14 | 0.443 | 138 (14) | 0.12 | <0.001 | 111 (11) | 24.40 | 0.001 | 138 (14) | 16.90 | <0.001 |
| <5 g/day | 311 (30) | 0.18 | | 287 (28) | 0.14 | | 311 (30) | 25.18 | | 287 (28) | 18.92 | |
| 5–29 g/day | 424 (42) | 0.18 | | 422 (41) | 0.18 | | 424 (42) | 31.05 | | 422 (41) | 20.87 | |
| ≥30 g/day | 169 (17) | 0.19 | | 169 (17) | 0.22 | | 169 (17) | 40.85 | | 169 (17) | 41.85 | |
| Missing information | 6 (1) | 0.34 | | 5 (0) | 0.21 | | 6 (1) | 144.56 | | 5 (0) | 19.27 | |
| Highest school level | | | | | | | | | | | | |
| None | 40 (4) | 1.10 | 0.008 | 40 (4) | 0.11 | <0.001 | 40 (4) | 23.9 | 0.182 | 40 (4) | 16.58 | 0.065 |
| Primary school | 357 (35) | 0.16 | | 335 (33) | 0.13 | | 357 (35) | 30.0 | | 335 (33) | 20.16 | |
| Technical/professional school | 276 (27) | 0.17 | | 273 (27) | 0.19 | | 276 (27) | 27.1 | | 273 (27) | 21.03 | |
| Secondary school | 123 (12) | 0.20 | | 142 (14) | 0.25 | | 123 (12) | 30.14 | | 142 (14) | 28.56 | |
| University | 181 (18) | 0.23 | | 181 (18) | 0.19 | | 181 (18) | 37.62 | | 181 (18) | 27.05 | |
| Missing information | 44 (4) | 0.15 | | 50 (5) | 0.15 | | 44 (4) | 37.62 | | 50 (5) | 16.14 | |

[a]$P$-value based on $t$-test and analysis of variance using geometric means of specific/total IgE values levels by baseline covariates.

alcohol consumption or body mass index (Supplementary Table 1, available at *Carcinogenesis* Online). The distribution of these variables in different lymphoma subtypes is presented in Supplementary Table 1, available at *Carcinogenesis* Online. Although there was no statistically significant difference between cases and controls regarding specific IgE levels, controls were more likely than cases to have levels of total IgE >20 and >100 kU/l, which indicate moderate and high probability of allergy symptoms, respectively ($P$ < 0.001; Supplementary Table 1, available at *Carcinogenesis* Online).

Table I presents the distributions and geometric means of total and specific IgE levels against inhalant antigens in lymphoma cases and controls, and by subject characteristics. Among both cases and controls, men had higher geometric means of total as well as specific IgE compared with women. Specific IgE levels among cases and controls and total IgE levels just among cases differed by age in both groups. Total and specific IgE levels varied widely between countries. Mean levels of total IgE in controls ranged from 18.8 kU/l in Norway to 40.3 kU/l in Italy. Mean levels in cases followed comparable patterns. With regard to subject characteristics, current smokers at the time of recruitment had considerably elevated total IgE levels for both cases and controls, whereas specific IgE levels were just slightly increased among the controls only. Increasing levels of alcohol consumption also correlated with increasing levels of total IgE among cases and controls, and with rising levels of specific IgE in cases only.

Table II provides risk estimates for the investigated lymphoid neoplasms and subtypes in relation to categories of specific and total IgE levels, adjusted for smoking, alcohol consumption and highest school level (in addition to matching factors). Specific IgE levels against inhalant antigens did not show any significant association with the combined risk estimate of the investigated lymphoid neoplasms, MM, B-NHL nor with the risks of specific B-NHL subtypes (DLBCL, FL and CLL; Table II).

When the analysis was restricted to cases diagnosed within the first 2 years following blood collection, a significant inverse association between specific IgE levels and overall risk of lymphoid neoplasms was observed in individuals positive for specific IgE (≥0.35 kU/I); OR = 0.52 (95% CI = 0.28–0.97), $P_{trend}$ = 0.022. No such association was observed among those diagnosed later than 2 years after baseline (Supplementary Table 2, available at *Carcinogenesis* Online).

Intermediate (20–100 kU/l) and high (>100 kU/l) levels of total IgE were associated with significant 28% ($P$ < 0.001) and 32% ($P$ = 0.004) reductions in risk for all studied lymphoid neoplasms, respectively ($P_{trend}$ = 0.974; Table II). These inverse associations were statistically significant for B-NHL [intermediate level: OR = 0.68 (95% CI = 0.53–0.88); high level: OR = 0.62 (95% CI = 0.44–0.86), $P_{trend}$ = 0.425] and MM [high level: OR = 0.40 (95% CI 0.21–0.79), $P_{trend}$ = 0.728; Table II]. Among the major B-NHL subtypes, the inverse relationship of cancer risk with increasing total IgE levels was restricted to CLL [intermediate level: OR = 0.49 (95% CI = 0.30–0.80); high level: OR = 0.13 (95% CI = 0.05–0.35), $P_{trend}$ = 0.042], but not seen for the risk of DLBCL and FL ($P_{heterogeneity}$ = 0.001; Table II). In total, it is worth noting that 19.9% of the B-NHL cases, 27.8% of the CLL cases, but only 13.3% of MM cases, had total IgE levels below the 10th percentile of the control distribution (data not shown).

Table III summarizes the results for CLL and MM risk in association with total IgE levels stratified by sex and time to diagnosis after baseline. Compared with the reference category (<20 kU/l), high total IgE (>100 kU/l) levels were associated with a significantly reduced CLL and MM risk for men [OR = 0.14 (95% CI = 0.05–0.45), $P_{trend}$ < 0.019; OR = 0.37 (95% CI = 0.15–0.94), respectively].



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**Table II.** Association of total prediagnostic IgE and specific IgE against inhalant antigens and the risk of lymphoid neoplasms overall and by subtype

| | Lymphoid neoplasms overall | | B-NHL | | DLBCL | | FL | | CLL | | MM | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of controls/cases | *P* | Number of controls/cases | *P* | Number of controls/cases | *P* | Number of controls/cases | *P* | Number of controls/cases | *P* | Number of controls/cases | *P* |
| | OR[a] (95% CI) | | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | | OR (95% CI) | |
| Total IgE (kU/l)[b] | | | | | | | | | | | | |
| Low, <20 | 413/495 | | 256/315 | | 52/57 | — | 50/54 | — | 75/113 | — | 95/111 | — |
| | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Intermediate, 20–100 | 410/361 | **<0.001** | 248/215 | **0.003** | 45/48 | 0.849 | 50/38 | 0.296 | 75/60 | **0.004** | 91/93 | 0.462 |
| | 0.72 | | 0.68 | | 1.06 | | 0.71 | | 0.49 | | 0.86 | |
| | (0.59–0.87) | | (0.53–0.88) | | (0.58–1.96) | | (0.38–1.35) | | (0.30–0.80) | | (0.56–1.30) | |
| High, >100 | 187/154 | **0.004** | 123/97 | **0.005** | 33/25 | 0.341 | 13/21 | 0.392 | 36/13 0.13 | **<0.00** | 39/21 | **0.009** |
| | 0.68 | | 0.62 | | 0.71(0.36–1.43) | | 1.44 | | (0.05–0.35) | **1** | 0.40 | |
| | (0.52–0.88) | | (0.44–0.86) | | | | (0.62–3.35) | | | | (0.21–0.79) | |
| $P_{trend}$ | 0.98 | | 0.425 | | 0.895 | | 0.164 | | **0.042** | | 0.728 | |
| Specific IgE (kU/l)[b] | | | | | | | | | | | | |
| <0.35 | 822/826 | — | 517/509 | — | 104/101 | — | 96/91 | — | 157/162 | — | 182/189 | — |
| | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| 0.35–1.06 | 62/66 | 0.717 | 31/41 | 0.233 | 11/13 | 0.869 | 7/6 | 0.820 | 4/7 | 0.371 | 16/15 | 0.857 |
| | 1.07 | | 1.35 | | 1.08 | | 0.86 | | 1.99 | | 0.93 | |
| | (0.74–1.55) | | (0.82–2.22) | | (0.43–2.74) | | (0.24–3.12) | | (0.46–8.54) | | (0.43–2.03) | |
| 1.07–4.33 | 64/59 | 0.681 | 37/41 | 0.602 | 9/10 | 0.818 | 2/9 | **0.024** | 12/8 | 0.312 | 14/8 | 0.251 |
| | 0.93 | | 1.14 | | 1.14 | | 7.64 | | 0.61 | | 0.59 | |
| | (0.64–1.34) | | (0.70–1.83) | | (0.38–3.46) | | (1.31–44.7) | | (0.24–1.54) | | (0.24–1.45) | |
| ≥4.33 | 62/59 | 0.721 | 42/36 | 0.448 | 6/6 | 0.700 | 8/7 | 0.930 | 13/9 | 0.330 | 13/13 | 0.940 |
| | 0.93 | | 0.83 | | 1.29 | | 0.95 | | 0.57 | | 0.97 | |
| | (0.64–1.37) | | (0.50–1.36) | | (0.36–4.66) | | (0.32–2.85) | | (0.19–1.78) | | (0.44–2.15) | |
| $P_{trend}$ | 0.219 | | 0.18 | | 0.133 | | 0.422 | | 0.069 | | 0.824 | |
| Specific IgE (kU/l)[b] | | | | | | | | | | | | |
| Negative ≤0.35 | 822/826 | — | 517/509 | | 104/101 | — | 96/91 | — | 157/162 | — | 182/189 | — |
| | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Positive >0.35 | 188/184 | 0.838 | 110/118 | 0.603 | 26/29 | 0.705 | 17/22 | 0.291 | 29/24 | 0.428 | 43/36 | 0.464 |
| | 0.98 | | 1.08 | | 1.14 | | 1.49 | | 0.77 | | 0.83 | |
| | (0.77–1.23) | | (0.80–1.47) | | (0.57–2.29) | | (0.71–3.14) | | (0.41–1.46) | | (0.50–1.37) | |

[a]Significant *P*-values are indicated in bold. OR and 95% CIs determined by conditional logistic regression. Model based on matching factors and adjusted for smoking status, alcohol consumption at recruitment and highest school level.

[b]Diagnostic cut points were used to identify positive and negative tests in kilounits of total and allergen-specific IgE antibody per liter (kU/l).

**Table III.** Association of total prediagnostic IgE and the risk of CLL and MM stratified by sex and time to diagnosis

| | <20 kU/l | | 20–100 kU/l | | | >100 kU/l | | | $P_{trend}$ |
|---|---|---|---|---|---|---|---|---|---|
| | Controls/ cases | OR[a] | Controls/ cases | OR[a] (95% CI) | *P*-value | Controls/ cases | OR[a] (95% CI) | *P* | |
| CLL | | | | | | | | | |
| Men | 33/58 | 1.00 | 38/35 | 0.56 (0.26–1.18) | 0.127 | 30/8 | 0.14 (0.05–0.45) | **<0.001** | **0.019** |
| Women | 42/55 | 1.00 | 37/25 | 0.52 (0.25–1.07) | 0.076 | 7/5 | 0.40 (0.04–4.15) | 0.442 | 0.473 |
| Cases <3 year after baseline | 24/38 | 1.00 | 21/16 | 0.23 (0.05–1.00) | **0.050** | 12/3 | 0.00 (0.00–0.21) | **0.008** | 0.060 |
| Cases ≥3 year after baseline | 51/75 | 1.00 | 54/44 | 0.54 (0.31–0.94) | **0.030** | 24/10 | 0.21 (0.07–0.63) | **0.005** | **0.044** |
| Cases <5 year after baseline | 39/59 | 1.00 | 36/31 | 0.51 (0.24–1.08) | 0.080 | 20/5 | 0.06 (0.01–0.39) | **0.003** | 0.051 |
| Cases ≥5 year after baseline | 36/54 | 1.00 | 39/29 | 0.53 (0.25–1.10) | 0.086 | 16/8 | 0.28 (0.08–0.97) | **0.044** | 0.195 |
| MM | | | | | | | | | |
| Men | 42/54 | 1.00 | 52/54 | 0.79 (0.42–1.50) | 0.473 | 26/12 | 0.37 (0.15–0.94) | **0.036** | 0.443 |
| Women | 53/57 | 1.00 | 39/39 | 0.99 (0.54–1.84) | 0.986 | 13/9 | 0.39 (0.12–1.28) | 0.122 | 0.941 |
| Cases <3 year after baseline | 30/44 | 1.00 | 29/24 | 0.46 (0.21–1.03) | 0.060 | 20/6 | 0.15 (0.04–0.60) | **0.007** | 0.062 |
| Cases ≥3 year after baseline | 65/67 | 1.00 | 41/69 | 1.05 (0.67–1.77) | 0.847 | 24/15 | 0.53 (0.23–1.22) | 0.134 | 0.471 |
| Cases <5 year after baseline | 55/71 | 1.00 | 51/51 | 0.74 (0.42–1.33) | 0.315 | 26/10 | 0.21 (0.08–0.59) | **0.003** | **0.042** |
| Cases ≥5 year after baseline | 40/40 | 1.00 | 40/42 | 0.95 (0.47–1.92) | 0.895 | 13/11 | 0.78 (0.27–2.25) | 0.642 | 0.197 |

[a]Significant *P*-values are indicated in bold. OR and 95% CIs determined by conditional logistic regression. Model based on matching factors and adjusted for smoking status, alcohol consumption at recruitment and highest school level.

Among women, those associations lacked statistical significance ($P$ = 0.442 and $P$ = 0.122, respectively). A significant inverse association between total IgE and CLL risk at the highest category of IgE levels compared with the reference value was observed among individuals diagnosed within 3 years of recruitment as well as those diagnosed later (<3 years: $P$ = 0.008; ≥3 years: $P$ = 0.005; $P_{heterogeneity}$ = 0.542, Table III). The inverse association remained significant when analysis was restricted to those diagnosed later than 5 years following recruitment ($P$ = 0.044).

Risk of MM was significantly associated with increasing levels of total IgE at the highest category of total IgE compared with the reference value in cases diagnosed <3 years after recruitment, but not later than 3 years. The test for heterogeneity was not statistically significant ($P_{heterogeneity}$ = 0.178).

## Discussion

We assessed the prospective relationship between allergies and lymphoid neoplasms using measurements of allergen-specific and total IgE in plasma as biomarkers of atopy and allergy. Although the levels of specific IgE against inhalant antigens as a marker for allergic/atopic diseases such as allergic rhinitis and asthma did not present any association with the risk of lymphoid cancers nor with lymphoma subtypes, we did observe a clear inverse relationship of total IgE levels with risk of investigated lymphoma subtypes overall and with the risk of CLL and MM in particular. The association of total IgE with risk of CLL remained statistically significant for cases diagnosed 5 or more years after blood collection. No significant relationship could be demonstrated between total IgE and risks of DLBCL and FL.

IgEs have an essential role in the allergic immune response. In addition, other functions of IgE have also been documented, e.g. in relation to immune surveillance and host defense (26). Total IgE levels vary greatly between individuals, and part of this variation is known to depend upon age, sex, race, seasonality, genetic factors, inflammatory processes and specific environmental exposures, including infections, smoking and alcohol consumption (the latter two reflected also in our data). IgE deficiency can either exist together with otherwise normal Ig levels (selective IgE deficiency), or in the context of a general hypo-gammaglobulinemia (mixed IgE deficiency) (27), which is characterized by very low plasma levels of IgE (<2.5 IU/ml), and is observed in only a small proportion of the population.

At least one case series in the USA, and case-control studies in Spain and Scandinavia have shown previously reduced levels of total IgE levels among CLL and MM patients compared with healthy adults (12,28–30). The United States study, which included only 43 patients in total, showed extremely reduced levels for a large proportion of patients, namely IgE levels below the 10th percentile of healthy adults for >60% of the CLL cases (28). In addition, the study reported that patients with CLL had significantly prolonged mean serum survival times of IgE and a decreased fractional catabolic rate, indicating that reduced IgE levels among these patients was likely the result of impaired IgE synthesis (28). Finally, the United States study also presented decreased IgE levels and synthesis rates for MM (28). The second study, in Spain, reported a significant inverse association between serum total IgE and lymphoma risk overall, and especially the risks of CLL, followed by MM and FL, in descending order (29). Furthermore, the inverse association was stronger for disease at a more advanced stage, in line with clinical observations that lymphoma patients, particularly those with CLL, are often affected by progressive immunodeficiency during the course of disease, and often present hypo-gammaglobulinemia of unknown origin (31,32). Likewise, the Scandinavian study reported low total IgE levels among cases with B-NHL, and particularly among cases with CLL/small lymphocytic lymphoma and lymphoblastic lymphomas, compared with controls (30). Apart from IgE, levels of other Ig subclasses (IgA, IgG and IgM) were also found to be reduced among the lymphoma cases in both the Spanish and the Scandinavian studies as well as in an Australian study (2,13), suggesting a generalized Ig suppression in patients with B-cell NHL (13,29,30). The effect appeared to be strongest for CLL cases, but the statistical power for subtype analysis was limited.

A Spanish case-control study by Ellison-Loschmann *et al.* (29) as well as a Scandinavian study (12), which included both a case-control and a prospective cohort component, have previously demonstrated inverse relationships between specific IgE, signifying a targeted immune response against inhalant allergens that are involved in allergic rhinitis and asthma, with overall lymphoma risk. The inverse relationship was restricted to lymphoma cases diagnosed <5 years after blood collection in the prospective component of the Scandinavian study, which was based on a Finnish maternity cohort, suggesting reverse causality as the underlying reason (12). Also in our study, when examining all lymphoid neoplasms together, we found a decreased OR in association with specific IgE positivity only for disease diagnosed within the first 2 years after blood collection [OR = 0.52 (95% CI = 0.28–0.97)], but not for longer follow-up periods [OR = 1.09 (95% CI = 0.85–1.41)].

Taken together, the overall results from our study and from other prospective biomarker studies so far, do not seem to support a protective role for specific IgE against lymphoma. In contrast, our data on total IgE do suggest that a more general relative degree of immunodeficiency might actually precede the clinical diagnosis of CLL



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by 5 or more years, as suggested by studies on CLL and possibly other lymphoma subtypes. With regard to very low levels of IgE, below the 10th percentile of the distribution among control subjects, our data showed that almost 30% of CLL cases presented with such low IgE levels. A high percentage (40.4%) of CLL cases diagnosed earlier than 3 years after baseline, but only 16.3% of those diagnosed 5 years or later after baseline had IgE levels below the 10th percentile of levels observed in the controls. In the United States Prostate, Lung, Colorectal and Ovarian Cancer Screening cohort, which analyses serially collected prediagnostic serum samples with lag times of up to 9.8 years prior to CLL diagnosis, only 3% of the case samples presented hypo-gammaglobulinemia prior to CLL diagnosis, and hypo-gammaglobulinemia was not seen at all until 3 years before the diagnosis of CLL (33). Severe inherited immunodeficiency is an established risk factor for NHL (34,35), but only a small proportion of cases can be explained by these rare primary immunodeficiency phenotypes. Secondary immunodeficiency, on the other hand, is a consequence of lymphomagenesis, mainly seen in more advanced stages of the disease. Reduced IgE levels several years prior to lymphoma diagnosis, as found in this and other studies, may suggest that moderate immunodeficiency constitutes a risk factor for CLL. However, prospective studies with long follow-up times, repeated blood samples and additional markers to quantify immunocompetence are required to firmly establish this relationship and rule out reverse causality. Experimental evidence exists that point towards a role of IgE in immune surveillance and tumor cell destruction (10). IgE antibodies to overexpressed tumor antigens have been shown to induce antibody-dependent cytotoxicity and phagocytosis, and IgE anticancer antibodies have been implicated in the destruction of ovarian cancer and pancreatic cancer cells by antibody-dependent cytotoxicity (36–38). Taken together, these observations suggest a contribution of IgE to tumor immune surveillance, and indeed, surface IgE appears to be a powerful adjuvant in antitumor immunity (39). Although antigen-specific IgE antibodies, and not total IgE, are thought to mediate most of these antitumor effects, total IgE may represent a proxy for an individual's general immune competence, including the capacity to form specific IgE anticancer antibodies. IgE is also known for its potential to dampen stimulation of B cells (40), which may offer another explanation for its putative protective effect. An important question is whether the inverse relationship particularly with CLL and MM rather than with other lymphoma subtypes may correlate with a longer duration of indolent forms of these specific subtypes that are associated with progressive immunodeficiency. This, again, would support the secondary immunodeficiency hypothesis outlined previously.

The strengths of this study include its prospective design with available prediagnostic plasma samples, state-of-the art detection of total IgE and specific IgE levels using ImmunoCAP 100 (Phadia, Uppsala, Sweden), a large sample size that allowed some subtype-specific analyses and matching for several variables with expected influence on IgE levels such as age, sex, date of blood withdrawal and length of follow-up. However, as a limitation, IgE levels were only assessed at a single time point, and hence, we could not assess whether the diagnosis of CLL was preceded by important individual longitudinal changes in IgE levels that differ from age-related changes seen among normal subjects. Our observations of increased total IgE levels in relation to smoking (positive) and alcohol consumption (positive) are in line with data from other studies (41,42) and speak in favor of the data quality. Another limitation of the study is that in spite of being the largest prospective study on the topic to our knowledge so far, power is limited. This applies in particular to the subtype and other stratified analyses involving cases of CLL and MM. Finally, a further limitation of our study is the missing classification of lymphoma subtypes in 71 cases, which led to a reduction of the sample size for the stratified analysis.

In conclusion, data of this prospective study do not support a risk decrease of lymphoma or single entities in relation to IgE biomarkers that are specific for allergic rhinitis and asthma. In contrast, we did observe considerably reduced total IgE levels among study participants who subsequently developed CLL. Although these reductions were visible even 5 or more years prior to clinical lymphoma diagnosis, we cannot rule out that lower total IgE levels are a proxy of a general hypo-gammaglobulinemia that has been frequently observed early on in the course of CLL. Future prospective studies should examine whether lymphoma risk is also preceded by long-term reductions in other classes of Igs, as more general markers of overall immune competence.

## Supplementary material

Supplementary Tables 1 and 2 can be found at http://carcin.oxfordjournals.org/

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## SupplementaryTable 1.

| Variable | Controls (%) | Cases (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | All cases | Subtypes of lymphoid neoplasms | | | | B-NHL subtypes | | |
| | | | HL | B-NHL | T-NHL | MM | DLBCL | FL | CLL |
| **Sex** | | | | | | | | | |
| Women | 495 (48.5) | 495 (48.5) | 21 (38.9) | 322 (50.8) | 10 (27.8) | 105 (46.5) | 65 (49.2) | 72 (62.1) | 85 (45.5) |
| Men | 526 (51.5) | 526 (51.5) | 33 (61.1) | 312 (49.2) | 26 (72.2) | 121 (53.5) | 67 (50.8) | 44 (37.9) | 102 (54.6) |
| **Age** | | | | | | | | | |
| <40 | 31 (3.0) | 31 (3.04) | 7 (13.0) | 15 (2.4) | 0 (0.0) | 5 (2.2) | 4 (3.03) | 2 (1.7) | 8 (4.3) |
| 40-49 | 141 (13.8) | 147 (14.4) | 13 (24.1) | 90 (14.2) | 8 (22.2) | 26 (11.5) | 23 (17.4) | 23 (19.8) | 22 (11.8) |
| 50-59 | 455 (44.6) | 451 (44.2) | 19 (35.2) | 293(46.2) | 12 (33.3) | 99 (43.8) | 58 (43.9) | 57 (49.1) | 86 (46.0) |
| 60+ | 394 (38.6) | 392 (38.4) | 15 (27.8) | 236 (37.2) | 16 (44.4) | 96 (42.5) | 47 (35.6) | 34 (29.3) | 71 (38.0) |
| **Education level**[a] | | | | | | | | | |
| None | 40 (3.9) | 40 (3.9) | 3 (5.6) | 27 (4.3) | 2 (5.6) | 7 (3.1) | 7 (5.3) | 4 (3.5) | 8 (4.3) |
| Primary School | 357 (35.0) | 335 (32.8) | 21 (38.9) | 203 (32.0) | 6 (16.7) | 83 (36.7) | 52 (39.4) | 34 (29.3) | 54 (28.9) |
| Technical/ Professional School | 276 (27.0) | 273 (26.7) | 15 (27.8) | 166 (26.2) | 10 (27.8) | 60 (26.6) | 35 (26.5) | 27 (23.3) | 48 (25.7) |
| Secondary School | 123 (12.1) | 142 (13.9) | 2 (3.7) | 98 (15.5) | 4 (11.1) | 31 (13.7) | 19 (14.4) | 21 (18.1) | 27 (14.4) |
| University | 181 (17.7) | 181 (17.7) | 12 (22.2) | 111 (17.5) | 11 (30.6) | 36 (15.9) | 12 (9.1) | 26 (22.4) | 43 (23.0) |
| **Alcohol consumption**[a] | | | | | | | | | |
| 0 g/d | 111 (10.9) | 138 (13.6) | 7 (13.0) | 91 (14.4) | 4 (11.4) | 26 (11.5) | 19 (14.6) | 17 (14.8) | 28 (15.0) |
| < 5 g/d | 311 (30.6) | 287 (28.3) | 16 (29.6) | 179 (28.4) | 3 (8.6) | 65 (28.8) | 37 (28.5) | 34 (29.6) | 51 (27.3) |
| 5-29 g/d | 424 (41.8) | 422 (41.5) | 20 (37.0) | 251 (39.8) | 18 (51.4) | 106 (46.9) | 46 (35.4) | 49 (42.6) | 75 (40.1) |
| 30 + g/d | 169 (16.7) | 169 (16.6) | 11 (20.4) | 110 (17.4) | 10 (28.6) | 29 (12.8) | 28 (21.5) | 15 (13.0) | 33 (17.7) |
| **Body Mass Index**[a,b] **(BMI)** | | | | | | | | | |
| Tertile 1 | 336 (32.9) | 335 (32.8) | 14 (25.9) | 223 (35.2) | 9 (25.0) | 64 (28.3) | 40 (30.3) | 44 (37.9) | 66 (35.3) |
| Tertile 2 | 349 (34.2) | 322 (31.5) | 22 (40.7) | 198 (31.2) | 11 (30.6) | 69 (30.5) | 32 (24.2) | 40 (34.5) | 63 (33.7) |
| Tertile 3 | 336 (32.9) | 364 (35.7) | 18 (33.3) | 213 (33.6) | 16 (44.4) | 93 (41.2) | 60 (45.5) | 32 (27.6) | 58 (31.0) |
| **Season of blood draw**[c] | | | | | | | | | |
| Spring | 294 (28.8) | 297 (29.1) | 19 (35.2) | 185 (29.2) | 9 (25.0) | 68 (30.1) | 43 (32.6) | 35 (30.2) | 52 (27.8) |
| Summer | 181 (17.7) | 183 (17.9) | 9 (16.7) | 125 (19.7) | 6 (16.7) | 36 (15.9) | 29 (30.0) | 19 (16.4) | 33 (17.6) |
| Autumn | 303 (29.7) | 299 (29.3) | 13 (24.1) | 169 (26.6) | 9 (25.0) | 79 (35.0) | 27 (20.5) | 39 (33.6) | 53 (28.3) |
| Winter | 243 (23.8) | 242 (23.7) | 13 (24.1) | 155 (24.4) | 12 (33.3) | 43 (19.0) | 33 (25.0) | 23 (19.8) | 49 (26.2) |
| **Specific IgE (kU/l)**[a] | | | | | | | | | |
| Negative (<0.35) | 830 (81.3) | 833 (81.6) | 44 (81.5) | 514 (81.1) | 27 (75.0) | 190 (84.1) | 103 (78.0) | 92 (79.3) | 163 (87.2) |
| Positive ( ≥ 35) | 191 (18.7) | 188 (18.4) | 10 (18.5) | 120 (18.9) | 9 (25.0) | 36 (15.9) | 29 (22.0) | 24 (20.7) | 24 (12.8) |
| **Specific IgE (kU/l)**[a] | | | | | | | | | |
| <0.35 | 831 (81.4) | 833 (81.6) | 44 (81.5) | 514 (81.1) | 27 (75.0) | 190 (84.1) | 103 (78.0) | 92 (79.3) | 163 (87.2) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 0.35-1.06 | 63 (6.2) | 69 (6.8) | 2 (3.7) | 43 (6.8) | 5 (13.9) | 15 (6.6) | 13 (9.9) | 8 (6.9) | 7 (3.7) |
| 1.07-4.33 | 64 (6.3) | 60 (5.9) | 2 (3.7) | 41 (6.5) | 3 (8.3) | 8 (3.5) | 10 (7.6) | 9 (7.8) | 8 (4.3) |
| ≥ 4.33 | 63 (6.2) | 59 (5.8) | 6 (11.1) | 36 (5.7) | 1 (2.8) | 13 (5.8) | 6 (4.6) | 7 (6.0) | 9 (4.8) |
| **Total IgE[a] (kU/l)** | | | | | | | | | |
| < 20 allergy unlikely | 416 (40.7) | 499 (48.9) | 21 (38.9) | 317 (50.0) | 18 (50.0) | 111 (49.1) | 58 (43.9) | 54 (46.6) | 113 (60.4) |
| 20 – 100 allergy possible | 415 (40.7) | 365 (35.8) | 18 (33.3) | 218 (34.4) | 10 (27.8) | 94 (41.6) | 49 (37.1) | 40 (34.5) | 60 (32.1) |
| >100 allergy very likely | 190 (18.6) | 157 (15.4) | 15 (27.8) | 99 (15.6) | 8 (22.2) | 21 (9.3) | 25 (18.9) | 22 (19.0) | 14 (7.5) |

**SupplementaryTable 2.**

| | Controls/Cases | < 2years OR[a] (95% CI) | p-value | Controls/Cases | ≥2 years OR (95% CI) | p-value |
|---|---|---|---|---|---|---|
| **Specific IgE (kU/l)** | | | | | | |
| Negative ≤0.35 | 154/166 | 1.00 | | 668/660 | 1.00 | |
| Positive >0.35 | 36/24 | 0.52 (0.28-0.97) | 0.039 | 152/160 | 1.09(0.85-1.41) | 0.497 |
| **p-trend** | | 0.022 | | | 0.540 | |
| **Specific IgE (kU/l)** | | | | | | |
| <0.35 | 154/166 | 1.00 | | 660/668 | 1.00 | |
| 0.35-1.06 | 10/13 | 1.13(0.45-2.81) | 0.800 | 52/53 | 1.06(0.70-1.59) | 0.782 |
| 1.07-4.33 | 11/8 | 0.54(0.19-1.51) | 0.239 | 53/51 | 1.01(0.67-1.51) | 0.977 |
| ≥4.33 | 15/3 | 0.11 (0.02-0.53) | 0.005 | 47/56 | 1.24(0.81-1.89) | 0.320 |
| **p-trend** | | 0.022 | | | 0.422 | |