

Atopy and Risk of Non-Hodgkin Lymphoma

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- Background** A possible connection between allergy and cancer has been suspected, but allergy-related conditions or atopy have been inconsistently associated with reduced risks of non-Hodgkin lymphoma. We investigated this association in a population-based case-control study and in a prospective study with prediagnostic blood specimens.
- Methods** We carried out a population-based study of 3055 case patients with non-Hodgkin lymphoma and 3187 control subjects in Denmark and Sweden, including questionnaire information on allergy and blood specimens, and a nested case-control study within a prospective cohort of more than 400 000 Finnish women. In the second study, serum specimens from the 198 case patients who developed non-Hodgkin lymphoma within a median of 8.9 years after the blood was drawn were matched with serum specimens from 594 control subjects. In both studies, laboratory-based evidence of allergy (atopy) was determined in serum on the basis of specific IgE reactivity to common inhalant allergens. Dissemination of disease was classified by the Ann Arbor system. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by logistic regression.
- Results** In the first study, ever having hay fever, but not other allergic conditions, was associated with a reduced risk of non-Hodgkin lymphoma. In particular, subjects with specific IgE reactivity in serum had a 32% (95% CI = 20% to 42%) lower risk of overall non-Hodgkin lymphoma than those without such reactivity. However, among case patients, dissemination of the disease was strongly inversely associated with specific IgE reactivity. In the second (i.e., prospective) study, no association was found between non-Hodgkin lymphoma and specific IgE reactivity, except possibly immediately before a diagnosis of non-Hodgkin lymphoma (≥ 10 years before diagnosis, OR = 1.00, 95% CI = 0.48 to 2.09; 5–9 years before, OR = 0.95, 95% CI = 0.50 to 1.84; 1–4 years before, OR = 0.33, 95% CI = 0.11 to 1.02; and < 1 year before, OR = 0.27, 95% CI = 0.03 to 2.31).
- Conclusion** Allergy may not be causally associated with the risk of non-Hodgkin lymphoma. The inverse association observed in some case-control studies may arise because non-Hodgkin lymphoma suppresses the immunologic response to allergens.

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The debate on a possible association between allergy and cancer is not recent (1–3). In an epidemiologic review of 66 studies published after 1985, Wang and Diepgen (4) concluded that “despite the mixed results ... allergy is associated with a reduced risk for cancer.” Allergy, being an atopic condition, can be regarded as a hyperreactive state of the immune system that reflects a shift in the T-lymphocyte response from an activity dominated by helper T cells type 1 to one dominated by helper T cells type 2. It has been hypothesized that this hyperreactive state might lead to increased tumor immunosurveillance, which would decrease the chance of proliferation of aberrant cells (5). However, evidence for such an explanation is lacking (6).

Particular interest has been given to the possible association between allergic conditions and non-Hodgkin lymphoma because this malignancy is very sensitive to immune modulation. In fact, the incidence of non-Hodgkin lymphoma may increase under certain immunosuppressive or immunostimulatory conditions.

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CONTEXT AND CAVEATS

Prior knowledge

An association between allergy and non-Hodgkin lymphoma has been suspected but not consistently found.

Study design

Large population-based retrospective case-control study (3055 case patients and 3187 control subjects) and prospective study with pre-diagnostic blood specimens (>400 000 women, of whom 198 developed non-Hodgkin lymphoma and 594 served as control subjects).

Contributions

The case-control study found that allergy was associated with a reduced risk of non-Hodgkin lymphoma, that specific IgE reactivity in serum was associated with lower lymphoma risk, and that among case patients, such reactivity was inversely associated with disease dissemination. The prospective study did not find an association between allergy and non-Hodgkin lymphoma, except possibly immediately before diagnosis.

Implications

Allergy may not be causally associated with non-Hodgkin lymphoma. The inverse association observed may arise because the disease suppresses the immunologic response to allergens.

Limitations

Selection bias cannot be completely excluded in the case-control study because nonparticipation between case patients and control subjects may have differed.

Primary and acquired immunodeficiency diseases, organ transplantation, autoimmune disease, and immunosuppressive therapy have been associated with increased risks of non-Hodgkin lymphoma (7,8). With respect to organ transplantation, it has been suggested that both the immunosuppressive effect of therapy and the antigenic stimulation of the immune system by the transplanted organ might result in abnormal proliferation of lymphocytes and an increased risk of non-Hodgkin lymphoma (8). In addition, both antigenic stimulation and the effect of immunosuppressive therapy may be involved in the development of non-Hodgkin lymphoma in patients with autoimmune disease (9,10).

Many studies investigating the association between allergic conditions and non-Hodgkin lymphoma have reported odds ratios (ORs) of approximately 1.0, indicating no association, or ORs of less than 1.0, indicating an inverse association (6,11–20). In particular, three large case-control studies—one among human immunodeficiency virus (HIV)-positive men (11)—found that risk of non-Hodgkin lymphoma was reduced by 35% to 70% among subjects with self-reported allergic rhinitis, hay fever, or food allergies (6,11,12). However, most studies have not found allergic conditions to be statistically significantly associated with non-Hodgkin lymphoma, and there has been little consistency in the patterns observed in the association between non-Hodgkin lymphoma and various atopic conditions (11–25).

Most published studies of the association between allergy and non-Hodgkin lymphoma can be criticized for using only self-reported history of allergy, which is prone to bias (24). Indeed, it is difficult to establish the precise distinction between allergic and nonallergic disease among subjects reporting a history of asthma

and certain skin conditions. We investigated the relationship between allergy and non-Hodgkin lymphoma in a population-based case-control study with both questionnaire and laboratory data on atopy status among case patients with incident non-Hodgkin lymphoma and control subjects. Findings from this study then led us to investigate this association in a case-control study nested in a large prospective cohort of Finnish women for whom prediagnostic blood specimens were available.

Materials and Methods

The Scandinavian Lymphoma Etiology Case-Control Study

Study Subjects. The Scandinavian Lymphoma Etiology (SCALE) study is a population-based case-control study of residents 18–74 years old who lived in Denmark from June 1, 2000, to August 30, 2002, or in Sweden from October 1, 1999, to April 15, 2002 (26). Patients with a first, newly diagnosed case of non-Hodgkin lymphoma, including chronic lymphocytic leukemia, were identified through a rapid case ascertainment network established in 157 hospital clinics in both countries, with backup from nationwide tumor registries; 3055 case patients were included in this study. Control subjects were randomly sampled from updated population registers and frequency matched on sex and age (in 10-year intervals) to the expected distribution of case patients with non-Hodgkin lymphoma in each country; 3187 control subjects were included. The participation rates were 81% among eligible case patients and 71% among control subjects. The study was approved by regional ethics committees in both countries. Written informed consent was obtained from each participant before interview and blood sampling.

Classification of Case Patients. In Denmark, review of tumor material took place within the Danish Lymphoma Registry Organization (27). In this registry, data from a random 10% sample of all case patients with incident lymphoma in the country are continuously reviewed by a panel of expert hematopathologists. Also, in all but 20% of the study case patients, the diagnostic tumor specimens had been evaluated primarily by a senior hematopathologist approved by the Danish Lymphoma Registry Organization. In Sweden, all case patients were histopathologically evaluated by one of six senior hematopathologists or cytologists and uniformly classified according to the World Health Organization classification system (28).

Questionnaire Data and Blood Specimens. Information on host characteristics, history of allergies and asthma, and potential confounding factors was collected during identical standardized telephone interviews in Denmark and Sweden. We interviewed 2505 (82%) of 3055 case patients within 6 months after the date of the diagnostic biopsy (median interval = 2.8 months; range = 0–40 months). Specifically, we obtained information about history of hay fever (allergy to pollen, animals [cats, dogs, or horses], house dust mites, or mold), childhood eczema, and asthma. We also recorded host characteristics, including birth order (first, second, or third or higher), educational level (7–9 years, 10–12 years, or ≥13 years of education), outdoor occupation lasting at least 1 year (ever or never), and occupation involving exposure to pesticides (yes or no) or to organic solvents (yes or no).

Serum was isolated from blood obtained from case patients, preferably before initiation of treatment for their diagnosed cancer. Serum was also isolated from whole blood obtained from control subjects. Serum from all participants was frozen at -80°C until testing.

Nested Case–Control Study in the Finnish Maternity Cohort With Prospectively Collected Blood Samples

The Finnish Maternity Cohort. To investigate the prospective nature of the association between atopy and non-Hodgkin lymphoma, we designed a nested case–control study within the Finnish Maternity Cohort of more than 400 000 Finish women (29,30), which has obtained blood samples from 98% of all pregnant women in Finland since 1983. The samples were taken in the first trimester of pregnancy for screening of congenital infections and stored at -25°C .

Identification of Case Patients with Non-Hodgkin Lymphoma and Control Subjects. Women in the Finnish Maternity Cohort who subsequently developed non-Hodgkin lymphoma were identified by linkage of the data files of the serum bank with the nationwide Finnish Cancer Registry. When more than one prediagnostic serum sample was available, the first (oldest) sample was chosen. For each of 198 identified case patients, we selected three control subjects, for a total of 594. Each control subject was alive and free of non-Hodgkin lymphoma at diagnosis of her corresponding case patient, and individually matched to her case patient by age at serum sampling (± 2 years) and length of serum storage (± 2 months).

Laboratory Analyses for Both Studies

Serum samples from both studies were analyzed for specific IgE with an enzyme-linked immunosorbent assay—i.e., the Phadiatop test (Phadia, Uppsala, Sweden)—to assess the following common inhalant allergens: grass (i.e., Timothy, g6); mugwort (w6), birch (t3); *Cladosporium herbarum* (m2); house dust mite (*Dermatophagoides pteronyssinus*, d1, and *Dermatophagoides farinae*, d2); cat (e1), dog (e2), and horse (e3) (31). All testing was performed without disclosing case patient or control subject status. The results are presented as total number of positive and negative results (cutoff value = <0.36 kU/L, according to the manufacturer's recommendation) and as a quantitative measure with the level of antibody response. Cut points for categorical variables were chosen on the basis of the distribution of control subjects and before the initiation of the association analyses. In trend tests, negative results were assigned the value 0.35 kU/L.

Statistical Analyses

To analyze SCALE data, we used unconditional multiple logistic regression. Results are presented as odds ratios, with 95% confidence intervals (CIs). All analyses were adjusted for the matching factors age (in 10-year intervals), sex, and country of residence. Potential confounders were considered on the basis of prior knowledge of risk factors for non-Hodgkin lymphoma, as well as on changes in the estimates when we compared models with and without additional covariates. The confounders included were birth order (categorical: first, second, or third or higher), education

(categorical by length of education: 7–9 years, 10–12 years, or ≥ 13 years), and outdoor occupation (yes or no) (see Table 2). Overall, the adjustments changed a few estimates by approximately 10% or less, and most estimates remained unchanged compared with the model that included only matching variables. Therefore, only estimates from the full model are presented.

Statistical significance of independent variables and interaction effects was tested by use of the likelihood ratio test. Trend tests were performed by use of the logarithm of the level of antibody response as the determinant. All tests of statistical significance were two-sided. Testing for homogeneity of effects over different outcomes used a data duplication method (32). This procedure allowed homogeneity to be assessed as the absence of an interaction between strata (labeling the different outcomes) and the determinant of interest (32).

The data from the Finnish Maternity Cohort were analyzed by use of conditional logistic regression to reflect the individual matching of case patients and control subjects. No further adjustments were made.

Results

The Scandinavian Lymphoma Etiology Case–Control Study

Overall, 3055 case patients of non-Hodgkin lymphoma and 3187 control subjects were enrolled in the study. A detailed distribution by age, sex, and country of residence is presented in Table 1 for control subjects and case patients with non-Hodgkin lymphoma, overall and by non-Hodgkin lymphoma subtypes that had more than 100 case patients. Table 1 also presents the distribution of information obtained by questionnaire on allergic conditions among control subjects and case patients, overall and by non-Hodgkin lymphoma subtype.

As shown in Table 2, self-reported allergic rhinitis (i.e., hay fever) was associated with a statistically significantly reduced risk of overall non-Hodgkin lymphoma (adjusted OR = 0.86, 95% CI = 0.77 to 0.98). There was also no statistically significant association between self-reported childhood eczema and non-Hodgkin lymphoma, overall or by any non-Hodgkin lymphoma subtype. Also, no association was found between self-reported asthma and non-Hodgkin lymphoma, overall or by subtype.

We also used blood specimens to analyze specific IgE reactivity with the Phadiatop test, which provides a more reliable indication of atopy than interview data. A blood specimen taken at the time of diagnosis (for case patients) or within 16 days (median) after interview (for control subjects) was available for 2670 case patients with non-Hodgkin lymphoma (i.e., 87.4% of case patients enrolled) and 2088 control subjects (i.e., 65.5% of control subjects enrolled). A total of 1059 blood specimens were obtained from case patients with non-Hodgkin lymphoma before treatment of their cancer, 829 specimens after initiation of treatment, and 782 specimens were obtained for which treatment information was not available. Eighteen percent of control subjects were positive for specific IgE compared with 13% of all case patients with non-Hodgkin lymphoma (Table 1). A detailed distribution by specific IgE serostatus and the quantitative level of specific IgE is presented for control subjects and for case

Table 1. General and disease characteristics of participants in the Scandinavian Lymphoma Etiology study according to case or control status, including case patients with non-Hodgkin lymphoma (NHL), overall and by NHL subtypes

Characteristic	Control subjects, No. (%)	All NHL	Case patients, No. (%)					
			NHL subtype*					
			Diffuse large B cell		Follicular		T cell	
							Marginal zone	Lympho-plasmacytic
Age†, y								
18–24	123 (4)	32 (1)	11 (1)	0	4 (1)	10 (5)	0	0,0
25–34	189 (6)	84 (3)	37 (5)	3 (0.5)	12 (2)	18 (9)	3 (3)	1 (1)
35–44	264 (8)	199 (7)	79 (10)	17 (2)	50 (9)	26 (13)	4 (3)	2 (2)
45–54	597 (19)	562 (18)	137 (17)	121 (16)	140 (24)	39 (19)	23 (20)	16 (14)
55–64	906 (28)	1008 (33)	244 (31)	259 (34)	210 (36)	55 (27)	40 (34)	44 (38)
65–74	1108 (35)	1170 (38)	288 (36)	352 (47)	170 (29)	56 (27)	47 (40)	53 (46)
Sex								
Male	1767 (55)	1819 (60)	474 (60)	480 (64)	279 (48)	128 (63)	57 (49)	75 (65)
Female	1420 (45)	1236 (40)	322 (40)	272 (36)	307 (52)	76 (37)	60 (51)	41 (35)
Country of residence								
Denmark	1186 (37)	1075 (35)	283 (36)	296 (39)	222 (38)	77 (38)	49 (42)	50 (43)
Sweden	2001 (63)	1980 (65)	513 (64)	456 (61)	364 (62)	127 (62)	68 (58)	66 (57)
Allergic rhinitis or hay fever‡								
No	2340 (74)	2362 (78)	617 (78)	583 (78)	436 (75)	160 (79)	93 (81)	97 (84)
Yes	815 (26)	658 (22)	170 (22)	161 (22)	142 (25)	42 (21)	22 (19)	18 (16)
Childhood eczema§								
No	2935 (94)	2856 (95)	737 (95)	705 (95)	548 (94)	188 (93)	112 (97)	109 (96)
Yes	202 (6)	151 (5)	39 (5)	37 (5)	32 (6)	14 (7)	3 (3)	4 (4)
Asthma‡								
No	2896 (91)	2791 (92)	725 (91)	689 (92)	547 (93)	181 (89)	107 (91)	99 (88)
Yes	275 (9)	251 (8)	68 (9)	60 (8)	39 (7)	22 (11)	10 (9)	14 (12)
Specific IgE totals								
Negative	1714 (82)	2325 (87)	574 (84)	606 (93)	441 (85)	138 (79)	91 (92)	91 (89)
Positive	372 (18)	341 (13)	110 (16)	43 (7)	76 (15)	37 (21)	8 (8)	11 (11)
Specific IgE levels, kU/L								
<0.36	1714 (82)	2325 (87)	574 (84)	606 (93)	441 (85)	138 (79)	91 (92)	91 (89)
0.36–0.99	105 (5)	125 (5)	40 (6)	23 (4)	22 (4)	12 (7)	4 (4)	4 (4)
1.00–4.99	138 (7)	124 (5)	34 (5)	16 (2)	35 (7)	12 (7)	3 (3)	6 (6)
≥5.00	129 (6)	92 (3)	36 (5)	4 (1)	19 (4)	13 (7)	1 (1)	1 (1)

* Only subtypes that had more than 100 cases were included in the table, which explains why values for the subtypes do not add up to the total.

† The group of chronic lymphocytic leukemia (CLL) also includes case patients with small lymphocytic lymphoma.

‡ Median age (range): control subjects = 59 y (18–76 y); all NHL = 60 y (18–74 y); diffuse large B cell = 60 y (19–74 y); CLL = 63 y (30–74 y); follicular = 57 (22–74 y); T cell = 55 y (18–74 y); mantle cell = 63 y (34–74 y); marginal zone = 62 y (26–74 y); and lymphoplasmacytic = 62 y (28–74 y).

§ Numbers do not necessarily add up to the total number of participants because some questions were left unanswered or, in the situation with specific IgE, because not all participants gave a blood specimen.

Table 2. Relative risk of non-Hodgkin lymphoma (NHL) overall and by subtype in relation to history of allergic conditions. Information from the Scandinavian Lymphoma Etiology study obtained by questionnaire and total and quantitative specific IgE level as measured in serum.*

Variable	NHL subtype, OR (95% CI)						
	All NHL, OR (95% CI)	Diffuse large B cell	CLL†	Follicular	T cell	Mantle cell	Marginal zone
From questionnaire†							
Allergic rhinitis							
or hay fever							
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	0.86 (0.77 to 0.98)	0.83 (0.68 to 1.00)	0.93 (0.76 to 1.14)	0.96 (0.78 to 1.18)	0.77 (0.54 to 1.11)	0.61 (0.38 to 0.98)	0.72 (0.44 to 1.18)
Childhood eczema							
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	0.92 (0.73 to 1.16)	0.87 (0.61 to 1.25)	1.08 (0.74 to 1.59)	0.99 (0.66 to 1.47)	1.01 (0.55 to 1.84)	0.83 (0.33 to 2.08)	0.53 (0.16 to 1.71)
Asthma							
No	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Yes	0.97 (0.81 to 1.17)	0.99 (0.75 to 1.32)	0.91 (0.67 to 1.23)	0.79 (0.55 to 1.12)	1.31 (0.82 to 2.09)	0.89 (0.47 to 1.69)	0.92 (0.46 to 1.86)
Blood‡							
Specific IgE total							
Negative	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Positive	0.68 (0.58 to 0.80)	0.83 (0.65 to 1.07)	0.36 (0.26 to 0.51)	0.79 (0.59 to 1.04)	1.09 (0.72 to 1.63)	0.82 (0.49 to 1.37)	0.49 (0.23 to 1.03)
Specific IgE							
level, kU/L							
<0.36	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
0.36–0.99	0.89 (0.68 to 1.17)	1.15 (0.78 to 1.70)	0.64 (0.40 to 1.04)	0.75 (0.45 to 1.23)	1.46 (0.77 to 4.76)	1.09 (0.51 to 2.33)	0.82 (0.29 to 2.32)
1.00–4.99	0.65 (0.50 to 0.85)	0.69 (0.46 to 1.02)	0.36 (0.21 to 0.61)	0.95 (0.64 to 1.42)	1.00 (0.53 to 1.89)	0.85 (0.38 to 1.89)	0.48 (0.15 to 1.56)
≥5.00	0.53 (0.39 to 0.70)	0.74 (0.49 to 1.12)	0.11 (0.04 to 0.30)	0.63 (0.38 to 1.05)	0.91 (0.47 to 1.76)	0.52 (0.19 to 1.46)	0.19 (0.03 to 1.38)
<i>P</i> _{trend}	<.001	.09	<.001	.10	.82	.20	.01

* Odds ratios (ORs) and 95% confidence intervals (CIs) from both questionnaire and blood test results were adjusted for age (in 10-year intervals), sex, country, birth order, education, and outdoor occupation. Only subtypes that had more than 100 cases were included in the table, which explains why values for the subtypes do not add up to the total.

† The group of chronic lymphocytic leukemia (CLL) also includes case patients with small lymphocytic lymphoma.

‡ Number of patients with NHL, overall and by subtype, with data from questionnaires available: all NHL = 3055; diffuse large B cell = 796; CLL = 752; follicular = 586; T cell = 204; Mantle cell = 148; marginal zone = 117; lymphoplasmacytic = 116.

§ The number of control subjects with a blood specimen was 2088. Number of patients with NHL, overall and by subtype, with serum available: all NHL = 2670; diffuse large B cell = 684; CLL = 651; follicular = 519; T cell = 175; mantle cell = 138; marginal zone = 99; lymphoplasmacytic = 102.

|| *P*_{trend} was calculated on the basis of the logarithm of the level of antibody response by use of a two-sided likelihood ratio test.

patients with non-Hodgkin lymphoma, overall and by subtypes in Table 1.

Subjects positive for specific IgE antibody were at 32% (95% CI = 20% to 42%) lower risk of overall non-Hodgkin lymphoma than seronegative subjects (Table 2). There was also a statistically significant inverse association between the quantitative antibody level of specific IgE and risk of overall non-Hodgkin lymphoma ($P_{\text{trend}} < .001$). With the exception of T-cell lymphomas, all odds ratios for the association between seropositivity to specific IgE and non-Hodgkin lymphoma subtypes were less than 1.0 (Table 2). For several subtypes, the reduction in risk was between 20% and 50%, but statistical significance was reached only for chronic lymphocytic leukemia. There was a statistically significant inverse association between the quantitative level of specific IgE antibodies and risk of chronic lymphocytic leukemia ($P_{\text{trend}} < .001$), marginal zone lymphomas ($P_{\text{trend}} = .01$), and lymphoplasmacytic lymphomas ($P_{\text{trend}} = .03$) (Table 2). The particularly strong association observed among the large group of case patients with chronic lymphocytic leukemia prompted us to perform a separate analysis of the association between being seropositive for specific IgE and the risk of overall non-Hodgkin lymphoma, excluding chronic lymphocytic leukemia. We found that the inverse association for overall non-Hodgkin lymphoma excluding chronic lymphocytic leukemia remained statistically significant (OR = 0.79, 95% CI = 0.66 to 0.94), as did that between the quantitative level of specific IgE and overall non-Hodgkin lymphoma excluding chronic lymphocytic leukemia ($P_{\text{trend}} = .003$).

We found no statistically significant heterogeneity among the seven non-Hodgkin lymphoma subtypes for self-reported allergic rhinitis ($P_{\text{homogeneity}} = .33$). In contrast, the association with specific IgE differed statistically significantly among non-Hodgkin lymphoma subtypes ($P_{\text{homogeneity}} < .001$) and among non-Hodgkin lymphoma B-cell subtypes ($P_{\text{homogeneity}} = .002$).

Age (<45 years or ≥ 45 years), sex (male or female), or country of residence (Denmark or Sweden) did not statistically significantly modify the association between self-reported allergic rhinitis and risk of overall non-Hodgkin lymphoma. These variables also did not modify the association between allergic rhinitis and non-Hodgkin lymphoma subtypes, with the exception of diffuse large B-cell lymphomas, for which a statistically significant inverse association with allergic rhinitis was found only among Danes ($P_{\text{interaction}} = .03$). There was also no interaction associated with age, sex, or country between specific IgE serostatus and risk of overall non-Hodgkin lymphoma or any non-Hodgkin lymphoma subtype.

We further evaluated whether the observed association varied between blood specimens obtained before and after initiation of cancer treatment. We found no effect modification by treatment status for the association with non-Hodgkin lymphoma overall (before treatment, OR = 0.75, 95% CI = 0.58 to 0.96, and after treatment, OR = 0.61, 95% CI = 0.44 to 0.84) or non-Hodgkin lymphoma B-cell types overall (before treatment, OR = 0.69, 95% CI = 0.53 to 0.90, and after treatment, OR = 0.58, 95% CI = 0.42 to 0.82). Among case patients with chronic lymphocytic leukemia, for whom the inverse association with specific IgE reactivity appeared strongest, treatment status was not associated with risk before treatment (OR = 0.33, 95% CI = 0.18 to 0.61) and after treatment (OR = 0.33, 95% CI = 0.10 to 1.10).

Finally, we investigated whether reactivity to specific IgE varied according to severity of disease at time of diagnosis (and blood collection). In this analysis, we included all 1339 case patients with non-Hodgkin lymphoma for whom we had detailed information on disease stage according to the Ann Arbor classification system (i.e., 1 = localized to 4 = widespread). Seropositivity to specific IgE was statistically significantly inversely associated with dissemination of disease (Ann Arbor stage 1 = 33 [number who were IgE seropositive]/154 [total number with this stage] or 21.4%; Ann Arbor 2 = 29/171 or 17.0%; Ann Arbor 3 = 29/199 or 14.6%; and Ann Arbor 4 = 74/815 or 9.1%; $P < .001$). An analysis of the risk of atopy that was associated with degree of dissemination of non-Hodgkin lymphoma determined by Ann Arbor stage and that was adjusted as in the former analyses for age, sex, country, birth order, education, and outdoor occupation found a stronger inverse association with more widespread disease (for Ann Arbor stages 1–4, respectively, OR = 1.01, 95% CI = 0.73 to 1.39; OR = 0.93, 95% CI = 0.65 to 1.33; OR = 0.81, 95% CI = 0.56 to 1.16; and OR = 0.52, 95% CI = 0.41 to 0.66). When non-Hodgkin lymphoma exclusive of chronic lymphocytic leukemia was analyzed, similar results were obtained (for Ann Arbor stages 1–4, respectively, OR = 1.04, 95% CI = 0.76 to 1.44; OR = 0.93, 95% CI = 0.65 to 1.33; OR = 0.82, 95% CI = 0.57 to 1.18; and OR = 0.61, 95% CI = 0.47 to 0.80). In both analyses, only the most extreme association was statistically significant.

The Finnish Maternity Cohort

Our findings from the SCALE study prompted us to investigate the association between risk of non-Hodgkin lymphoma and seropositivity to specific IgE in prediagnostic specimens from the prospective Finnish Maternity Cohort. Samples were available from 198 patients who developed non-Hodgkin lymphoma within a median of 8.9 years after blood collection. These specimens, along with those from 594 matched control subjects, were tested for specific IgE reactivity. Overall, non-Hodgkin lymphoma was associated with a statistically nonsignificant decreased risk of being atopic (OR = 0.74, 95% CI = 0.48 to 1.15). However, as shown in Table 3, the inverse association was restricted to serum specimens obtained shortly before non-Hodgkin lymphoma diagnosis (samples obtained ≥ 10 years before diagnosis, OR = 1.00, 95% CI = 0.48 to 2.09; 5–9 years before, OR = 0.95, 95% CI = 0.50 to 1.84; 1–4 years before, OR = 0.33, 95% CI = 0.11 to 1.02; and <1 year before, OR = 0.27, 95% CI = 0.03 to 2.31). Thus, we found no evidence of an association between atopy and non-Hodgkin lymphoma in specimens obtained 10 or more years or 5–9 years before the diagnosis of non-Hodgkin lymphoma. Close to the date of diagnosis, there was a tendency toward an inverse association that, however, did not reach statistical significance (Table 3).

Discussion

The findings from this study argue strongly against a causal association between allergic conditions or atopy and non-Hodgkin lymphoma as previously hypothesized (11). Instead, we hypothesize that the inverse association observed in some case-control studies arises because non-Hodgkin lymphoma suppresses the immunologic response to allergens.

We were initially intrigued by our finding in the SCALE study of a strong inverse association between laboratory-confirmed

Table 3. Association between reactivity to specific IgE against inhalant allergens and non-Hodgkin lymphoma (NHL) in serum specimens obtained in different time intervals before NHL diagnosis: a case-control study nested in the Finnish Maternity Cohort

Time before NHL diagnosis, y	No. of case patients (No. with specific IgE seropositivity)	No. of control subjects (No. with specific IgE seropositivity)	OR (95% CI)*
<1	10 (1)	32 (10)	0.27 (0.03 to 2.31)
1–4	31 (4)	84 (27)	0.33 (0.11 to 1.02)
5–9	77 (15)	230 (49)	0.95 (0.50 to 1.84)
≥10	80 (14)	248 (41)	1.00 (0.48 to 2.09)

* OR = odds ratio; CI = confidence interval.

type 1 allergy, as measured by the Phadiatop test, and risk of non-Hodgkin lymphoma. Overall, the risk of non-Hodgkin lymphoma was about one-third lower among subjects with specific IgE reactivity than among those without such reactivity. Of seven non-Hodgkin lymphoma subtypes, all but T-cell lymphomas were inversely associated with specific IgE seropositivity, and the inverse association between levels of specific IgE antibodies and risk of overall non-Hodgkin lymphoma was statistically significant. A similar trend was observed for all non-Hodgkin lymphoma subtypes, again with the exception of T-cell lymphomas, that reached statistical significance for chronic lymphocytic leukemia, lymphoplasmacytic lymphomas, and marginal zone lymphomas and reached borderline statistical significance for follicular lymphomas. However, a possible interpretation of these results as indicating causality was challenged by further findings of a statistically significant inverse association between the dissemination of non-Hodgkin lymphoma disease at time of blood collection and seropositivity to specific IgE. Impaired humoral immunity has previously been associated with severity of hematologic neoplasia (33). Thus, these latter results would be consistent with a situation in which persons with widespread lymphoma of B-cell but not T-cell origin had a reduced ability to mount a response to allergens. Hence, reverse causality might arise if IgE negativity were a consequence of the disease status rather than its cause.

To substantiate this suspicion, we then performed a prospective investigation with a nested case-control study in the Finnish Maternity Cohort. With the exception of specimens taken in the years immediately preceding the cancer diagnosis, there was no indication that subjects who were seropositive for specific IgE were at different risk of developing non-Hodgkin lymphoma than subjects who were seronegative for such specific IgE antibodies. In line with these results, a recent Swedish study linking a clinical database of specific IgE results to the national cancer registry found no association with cancer overall. The study appeared too small for an analysis of specific tumor sites in any great detail; however, the authors reported that lymphomas in general did not appear to be associated with specific IgE reactivity (34). Theoretically, our finding of an inverse association with specific IgE only among case patients immediately preceding their diagnosis with non-Hodgkin lymphoma could be interpreted as an etiologic link between atopy and non-Hodgkin lymphoma but with a very short incubation period. In fact, in association with immunosuppressive conditions, non-Hodgkin lymphoma has been reported to sometimes have short incubation periods (8). However, such an interpretation would not easily explain our finding of a strong association between specific IgE seronegativity and the

degree of dissemination of non-Hodgkin lymphoma. Instead, it is far more likely that reverse causality explains the inverse association observed in our studies.

We found that self-reported allergic rhinitis was associated with a reduced overall risk of non-Hodgkin lymphoma. However, the association was not strong for non-Hodgkin lymphoma overall or for specific subtypes. Almost all previous studies (14–20) on atopic disease have been based on self-reported information and have found conflicting results, either no association between atopic disease and non-Hodgkin lymphoma or a statistically nonsignificant inverse risk association. In their case-control study from San Francisco, Holly and Lele (11) found a statistically significantly threefold reduced risk of non-Hodgkin lymphoma among HIV-positive homosexual men reporting allergic rhinitis. The same investigators found anti-histamine use to be inversely associated with the risk of non-Hodgkin lymphoma. Canadian researchers have reported that allergy desensitization shots were associated with 50% reduction in non-Hodgkin lymphoma risk (35). Most studies that investigated the association between allergies to specific allergens and non-Hodgkin lymphoma risk found either no association (with ORs of ~1.0) (12,14,16) or an association with reduced risk that just reached statistical significance (12,13). We also found no indication that allergic manifestations taking place early in life—e.g., childhood eczema (atopic dermatitis) or early-onset hay fever—were associated with non-Hodgkin lymphoma. Thus, our finding of a lower prevalence of allergic rhinitis among case patients with non-Hodgkin lymphoma than among population control subjects may reflect a recent decline in clinical manifestations of allergic conditions as a result of underlying non-Hodgkin lymphoma disease.

Although enrollment rates in the SCALE study were relatively high among both case patients (81%) and control subjects (71%), reasons for nonparticipation may have differed, and among case patients particularly, nonparticipation may have been because of death. It appears unlikely that nonparticipation would be differently linked to allergy-related conditions among case patients and control subjects. However, we cannot exclude the possibility that the small group of nonparticipating case patients may have differed with respect to severity of disease. Such a selection bias would, if anything, tend to underestimate the already strong inverse association between specific IgE seropositivity and risk of lymphoma and, therefore, have no bearing on the overall result of the study. In our analysis of the effect of cancer treatment on the detection level of IgE seropositivity, we lacked treatment information on 29% of the case patients. We are not aware of any systematic error in obtaining such information but cannot rule out the possibility that the

group missing treatment information may have been different from the one with treatment information.

Strengths of our investigation include the large size of the SCALE study, its population-based design, its rapid case ascertainment, its thorough and uniform classification of case patients with non-Hodgkin lymphoma according to World Health Organization criteria (28), and its capacity to evaluate associations with several subtypes of non-Hodgkin lymphoma. However, crucial for the interpretation was the prospective nature of our second nested case-control study. This study included prospectively collected prediagnostic blood samples on all case patients with non-Hodgkin lymphoma in the Finnish Maternity Cohort, which represents 98% of all Finnish women, and blood samples from a matched control group. Although smaller in size, the study had information of high quality that with much certainty is free from differential misclassification and selection bias.

Most important, however, was our ability to assess atopy status on the basis of serologic testing rather than exclusively on interview data, which are susceptible to bias. In contrast to total IgE, which is poorly associated with allergic conditions, the detection and titration of allergen-specific IgE determined by the Phadiatop test have proven to be of great clinical relevance. A study comparing results obtained with the Phadiatop test with the clinical diagnosis of atopy in patients with allergic rhinitis and asthma found that the Phadiatop test had a specificity of 91%–94% and a sensitivity of 89%–96% (31).

In conclusion, we found that patients with B-cell but not T-cell non-Hodgkin lymphoma were statistically significantly less likely than population control subjects to have antibodies against specific IgE. Furthermore, we found that the inverse association increased with increasing dissemination of disease and that it was only found among patients with prediagnostic specimens immediately preceding non-Hodgkin lymphoma diagnosis. Thus, non-Hodgkin lymphoma development may suppress the immunologic response to allergens, and the association between atopic conditions and non-Hodgkin lymphoma may most likely be explained by inverse causality.

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