Allergies and Risk of Non-Hodgkin's Lymphoma by Subtype

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Abstract

To investigate the relation between allergy and risk for non-Hodgkin's lymphoma (NHL), data were analyzed from the Selected Cancers Study. Cases ($n = 952$) were men ages 32–60 years diagnosed with NHL from 1984 to 1988 and identified by eight population-based United States cancer registries. Controls ($n = 1691$) were recruited by random-digit telephone dialing and frequency matched to cases by age and geographic region of cancer registry. Logistic regression was used to calculate odds ratios and 95% confidence intervals adjusted for age, cancer registry, education, and race/ethnicity. There was no evidence that a general history of allergy was significantly associated with either overall NHL risk (odds ratio: 1.0; 95% confidence interval: 0.8–1.2) or risk for major NHL subtypes (follicular, diffuse, small cell lymphocytic, and immunoblastic). Similarly, no significant associations were observed for the most commonly reported specific allergies, including those to plants, dust, food, animals, and medications. Significant NHL subtype-specific associations were found for allergies to insects (immunoblastic) and chemicals (diffuse and small cell lymphocytic). However, these allergies were reported by relatively few study participants, and the associations may have been because of chance. In conclusion, we found little evidence that either a general history of allergy or commonly reported specific allergies are associated with NHL.

Introduction

NHL[2] is the fifth most common malignant neoplasm in the United States, with an estimated 56,200 new cases projected for the year 2001 (1). Over the last few decades, the incidence of NHL has increased rapidly throughout the world (2, 3). However, apart from HIV infection, a relatively minor contributor to the increase, reasons for the rise in NHL remain obscure (4, 5).

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[2] The abbreviations used are: NHL, non-Hodgkin's lymphoma; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; OR, odds ratio; CI, confidence interval.

A history of allergy or allergy-related conditions has been widely studied as a potential risk factor for NHL, but findings from at least 17 previous studies (6–22) have been contradictory (Table 1). Although several reports have described a significant decrease in risk for NHL among persons with a history of allergies (6–9), others have reported significant increases in risk (10–14), and many have not detected any type of association (15–22).

This may reflect, in part, the spectrum of lymphoproliferative diseases across which NHL findings have sometimes been reported. In four studies (8, 11, 12, 14), including two of three prospective studies (11, 12), data were analyzed for cases of NHL that had been combined with cases of Hodgkin's disease, leukemia, and/or multiple myeloma. Further inconsistency exists in the type of allergies and allergic conditions for which NHL associations have been investigated. In many studies (8, 12, 15, 16, 18, 20–22), only a single summary measure of association has been reported for a multitude of specific allergies that were combined into one group, sometimes together with a variety of nonspecific allergy-related conditions, including asthma, hay fever, urticaria (hives), angioneurotic edema, eczema, and contact dermatitis. A few studies looking at allergy and NHL have reported associations exclusively for nonspecific allergy-related conditions (10, 14, 19), including those like eczema and contact dermatitis, which are often attributable to causes other than allergy.

Several studies have looked at associations for specific allergies (6, 7, 9, 11, 13). However, there has been considerable inconsistency in the allergies for which associations have been investigated and the degree of specificity with which these allergies have been defined. For example, whereas some investigators have looked at food allergies as a group (6, 7, 13), others have focused only on specific food allergies (9). Similarly, associations have variably been examined either for allergies to insect bites/stings as a group (9) or only for specific insect allergies, such as those to bee stings (11). Even in case control studies, this increased specificity has often been at the expense of markedly reduced precision in risk estimates because of limitations on sample size. Moreover, estimates of risk from case control studies have frequently been reported without adjustment either for important confounders or for selection bias, which can be introduced by matching (23). The importance of adjustment for confounding is underscored by prospective data suggesting that protective effects of allergy seen in case control studies may "be partially explained by the confounding factors of age, sex, smoking, and race" (12).

We have attempted to address these methodological limitations by investigating the relation between 10 specific physician-diagnosed allergies and risk of NHL stratified by subtype, using data from the Selected Cancers Study (24, 25).

Materials and Methods

The Selected Cancers Study was a large population-based case control study designed to investigate associations between exposure to Agent Orange during United States military service in

Table 1 Findings from previous studies reporting associations between allergy and NHL[a]

Reference	Study type	Histology	Allergy type	RR/OR[b] (95% CI)	Comments[c]
McCormick *et al.* (22) (1971)	Case control (HB)	Lympho-sarcoma	Nonspecific	1.2 (0.4–4.1)[d]	Nonspecific allergy includes "hives, asthma, hay fever, contact dermatitis, angioneurotic edema, food allergy, childhood eczema, or drug reactions." Matching on age (range unspecified) and sex; OR unadjusted.
Bernard *et al.* (14) (1984)	Case control (HB)	NHL, HD, lymphoid leukemia	Contact dermatitis Eczema Eczema + contact dermatitis	2.0 (0.5–7.9) 4.5 (1.4–14.3) 3.8 (1.6–9.1)	Matching on age (range unspecified), sex, and geographic region; ORs unadjusted.
Tielsch *et al.* (21) (1987)	Case control (HB)	NHL	Cumulative allergy index	1.3 (0.6–2.8)	Directly interviewed cases and controls matched on age, sex, race, and year of diagnosis; unadjusted OR for index defined by total number of allergic conditions, including specific allergies (drugs, food, insect stings, and other), hay fever, asthma, eczema, hives, and history of injection therapy for allergies.
McWhorter *et al.* (12) (1988)	Prospective	Lymphoma leukemia, myeloma	Nonspecific Hives (any) Hives (≥5 yr)	3.8 (1.6–9.5) 7.9 (3.1–19.9) 9.3 (3.7–23.6)	Self-reported data for "physician-diagnosed" allergic conditions from NHANESI; nonspecific allergy includes "asthma, hay fever, hives, food allergy, or other allergies." RRs adjusted for age, sex, race, and smoking status. RR for any hives, unqualified by physician diagnosis: 7.4 (2.6–21.3).
Cartwright *et al.* (13) (1988)	Case control (HB)	NHL	Nonspecific Food Medication Metals Pollen/dust Soap Sunlight Eczema dermatitis	<2.0 (ns) <2.0 (ns) <2.0 (ns) <2.0 (ns) <2.0 (ns) <2.0 (ns) <2.0 (ns) 1.6 (1.1–2.4)	Self-reported data "cross-checked with both hospital records and general practitioner notes." Matching on age (+/− 3 yrs), sex, and residential health district; ORs for nonspecific and specific allergies reported as "nonsignificant results with risk ratios under 2.0" stratified by age (15–64 yr, ≥65 yr) and sex; OR for eczema dermatitis unadjusted, but "stratification of analyses confirm these findings, although smaller numbers in certain subgroups do not achieve statistical significance."
Franceschi *et al.* (20) (1989)	Case control (HB)	NHL	Nonspecific	1.0 (0.6–1.5)	Nonspecific allergy includes asthma, eczema, medication allergies, and food allergies; OR adjusted for age and sex.
Doody *et al.* (19) (1992)	Case control (HMOB)	NHL	Eczema Hay fever	1.9 (0.6–5.8) 0.5 (0.2–1.2)	Data abstracted from medical records of health maintenance organization for cases and controls matched on age, sex, region, and duration of membership; ORs unadjusted (ORs adjusted for sex and region not reported given no "meaningful difference").
Bernstein *et al.* (9) (1992)	Case control (PB)	NHL	Aerosol sprays: M/F Animal furs: M/F Cleaning agents: M/F Detergents: M/F Eggs: M/F Fabric: M/F Insect bites/stings: M/F Jewelry/metals: M/F Milk products: M/F Nuts and berries: M/F Other foods: M/F Soaps/perfumes: M/F Pollens/dusts: M/F Other allergies: M/F Eczema: M/F Hay fever: M/F Hives: M+F	2.3 (0.7–7.5)[d]/0.7 (0.4–1.4)[d] 1.2 (0.6–2.2)[d]/0.9 (0.5–1.3)[d] 2.1 (0.7–6.3)[d]/1.0 (0.5–1.8)[d] 1.2 (0.6–2.4)[d]/1.1 (0.7–1.7)[d] 1.1 (0.7–1.7)[d]/1.2 (0.8–1.7)[d] 1.5 (0.9–2.5)[d]/1.1 (0.8–1.6)[d] 0.9 (0.4–1.8)/0.6 (0.4–1.0) 0.6 (0.2–1.9)[d]/1.0 (0.6–1.7)[d] 1.0 (0.3–3.5)[d]/1.2 (0.6–2.5)[d] 0.4 (0.2–1.0)/0.8 (0.5–1.4) 1.1 (0.5–2.1)[d]/1.2 (0.7–2.1)[d] 0.8 (0.5–1.4)[d]/1.0 (0.7–1.5)[d] 1.2 (0.8–1.7)[d]/1.1 (0.8–1.4)[d] 1.0 (0.6–1.4)[d]/1.1 (0.7–1.5)[d] 0.6 (0.3–1.2)/0.6 (0.3–1.2) 1.0 (0.7–1.6)[d]/1.0 (0.7–1.4)[d] 1.2 (1.0–1.6)	Cases and controls matched on age (+/−5 years), sex, race, and neighborhood of residence of case at time of diagnosis; 15 specific allergy categories included in study. Unadjusted sex-stratified ORs selectively reported for allergies to nuts and berries, insect bites/stings, eczema, and hives. Secondary analyses not done for allergies reported by <10 study participants.
La Vecchia *et al.* (18) (1992)	Case control (HB)	NHL	Nonspecific	1.0 (0.6–2.1)	Nonspecific allergy "includes drug and food allergies, asthma, and eczema." OR adjusted for age and sex.

Table 1 Continued

Reference	Study type	Histology	Allergy type	RR/OR[b] (95% CI)	Comments[c]
Mills *et al.* (11) (1992)	Prospective	Lymphoma	Nonspecific 1 allergy 2 allergies ≥3 allergies Bee sting Chemicals Medication Poisonous plants Asthma Hay fever	1.7 (1.0–3.1) 2.2 (1.2–4.1) 1.3 (0.5–3.4) 1.8 (0.6–5.2) 1.1 (0.4–3.7) 1.3 (0.3–5.4) 1.6 (0.8–3.1) 1.5 (0.8–3.0) 0.4 (0.0–2.5) 1.0 (0.4–2.3)	Self-reported data for "asthma, hay fever, and reactions to medications, chemicals, bee sting, and poison oak (or ivy) or other plants" . . . "sufficiently serious to require treatment from a physician" Cohort exclusively comprised of Caucasian, non-Hispanic Seventh-Day Adventists; RRs adjusted for age, sex, smoking history, and time since last physician visit. $P = 0.21$ for linear trend.
Eriksson *et al.* (17) (1995)	Prospective	NHL	Atopy Atopic Intermediate Nonatopic Asthma Hives Rhinitis	 3.8 (0.5–13.8)[e] 3.4 (0.4–12.2)[e] 1.7 (0.2–6.3)[e] 1.0 (0.0–5.8)[e] 0.0 (0.0–13.6)[e] 2.9 (0.8–7.5)[e]	Atopy status based on response to challenge with eight selected plant and animal allergens using a skin prick test. Cohort consisted of patients who were skin prick tested at the allergy clinic of Central Hospital in Halmstad, Sweden. Standardized incidence ratios for NHL derived from expected age- and sex-specific incidence rates for region using data from Swedish Tumor Registry.
Petroianu *et al.* (8) (1995)	Case control (HB)	Lymphoma	Nonspecific	0.2 (0.1–0.7)[d]	Cases and controls matched on sex. Controls were "students of the medical school and teachers of the same institution, relatives and friends of the authors." OR unadjusted.
Holly *et al.* (7) (1997)	Case control (PB)	NHL	Nonspecific: HIV+/HIV− Animals: HIV+/HIV− Dust: HIV+/HIV− Food: HIV+/HIV− Plants: HIV+/HIV−	0.5 (0.3–0.8)/0.3 (0.2–0.6) 0.5 (0.2–1.3)/0.4 (0.1–1.5) 0.3 (0.1–0.7)/0.4 (0.1–1.6) 0.9 (0.4–1.8)/0.3 (0.1–0.9) 0.3 (0.2–0.6)/0.5 (0.2–1.1)	Cases and controls comprised of homosexual men matched on age (+/− 5 yrs) and county of residence; ORs adjusted for age. Nonspecific allergy excludes medication; plant allergy includes grass, hay, leaves, and pollen; dust allergy includes allergies to chalk and mold.
Holly *et al.* (6) (1999)	Case control (PB)	NHL	Animals: M/F Dust: M/F Food: M/F Medication: M/F Plants: M/F Asthma: M/F Hives: M/F	0.5 (0.3–0.8)/0.7 (0.5–1.1) 0.9 (0.6–1.3)/0.7 (0.4–1.0) 1.0 (0.7–1.3)/0.8 (0.6–1.0) 1.0 (0.8–1.3)/0.8 (0.6–0.9) 0.6 (0.4–0.8)/0.5 (0.4–0.7) 0.9 (0.6–1.2)/0.8 (0.5–1.2) 1.2 (0.9–1.5)/0.6 (0.5–0.8)	Cases and controls comprised of heterosexual men and women matched on age (+/−5 yrs), sex, and county of residence; sex-stratified ORs adjusted for age; plant allergy includes allergies to grass, hay, leaves, and pollen; dust allergy includes allergies to chalk and mold.
Vineis *et al.* (15) (2000)	Case control (PB)	NHL	Nonspecific Eczema Hay fever	0.9 (0.7–1.3) 1.2 (0.9–1.6) 0.7 (0.5–1.0)	Analyses restricted to study participants who recalled date of diagnosis. ORs adjusted for age and sex.
Tavani *et al.* (16) (2000)	Case control (HB)	NHL	Nonspecific Asthma	0.9 (0.7–1.2) 0.8 (0.5–1.4)	Nonspecific allergy includes allergies to medication and food. ORs adjusted for age, sex, and education.
Fabbro-Peray *et al.* (10) (2001)	Case control (HB)	NHL	Asthma Eczema Hives	0.8 (0.5–1.3) 0.5 (0.3–0.7) 1.7 (1.2–2.2)	ORs adjusted for age, sex, education, urban/rural residence, selected risk factors related to medical and occupational history, and for each other.

[a] Studies are ordered chronologically by year of publication. Abbreviations: HB, hospital based; HD, Hodgkin's disease; HIV+/HIV−, HIV+ homosexual men/HIV− homosexual men; HMOB, health maintenance organization based; M/F, male/female; NHANESI, First National Health and Nutrition Examination Survey; ns, nonsignificant ($P = 0.05$); PB, population based.
[b] Relative risk (RR)/OR and 95% CI. For consistency, values for risk estimates are rounded to nearest single decimal place (or to nearest even single decimal place in event of equidistance).
[c] Unless otherwise noted, information on history of allergy and allergic conditions was self reported by study participants without qualification of a physician diagnosis.
[d] OR and 95% CI not reported. Unadjusted OR and 95% CI calculated using published frequency data.
[e] Standardized incidence ratios and 95% CIs.

Vietnam and the development of cancer. Methods have been described in detail elsewhere (24, 25). Briefly, eligible cases were men born between 1929 and 1953 with an initial diagnosis of lymphoma between 1984 and 1988. Cases were identified from eight population-based cancer registries: five covered United States metropolitan areas (Atlanta, Miami, Detroit, Seattle, and San Francisco) and three covered states (Connecticut, Iowa, and Kansas). All registries, except those in Miami and Kansas, were part of the Surveillance, Epidemiology, and End Results program. A rapid case reporting scheme was used to obtain interviews as soon as possible after diagnosis. Controls were identified by random-digit telephone dialing and frequency matched to cases by 5-year date-of-birth intervals and geographic location of cancer registry.

Of 2,354 cases with an initial diagnosis of NHL, Hodgkin's disease, or "lymphoma not otherwise specified," 2,073 (88.1%) participated (Table 2). For 97% of these cases, microscopic slides or tissue blocks could be obtained from the

Table 2 Selection of NHL cases and controls, selected cancers study, 1984–1988

Selection step	Cases	Controls
Lymphoma cases[a]/controls[b]	2354	2299
Interviewed[c]	2073	1910
Pathology specimen obtained	2004	
Lymphoma diagnosis confirmed[d]	1868	
Unclassifiable	14	
Hodgkin's disease confirmed	343	
NHL confirmed	1511	
Excluded from analysis[e]		
Acquired immunodeficiency syndrome	290	1
Proxy interview	274	0
Interview quality/interviewee cooperation suboptimal	116	113
Major risk factor for AIDS	44	57
Incomplete allergy history	27	53
Total study population	952	1691

[a] All cancer registry cases with initial diagnosis of NHL, Hodgkin's disease, or "lymphoma not otherwise specified."
[b] 91.4% (14,328/15,768) of households contacted by random-digit dialing provided eligibility information, 90.9% (4,381/4,822) with eligible men provided name and address, from which 2,299 men were randomly selected.
[c] 11.9% of cases and 16.9% of controls declined study participation, most often because of refusal to be interviewed.
[d] Confirmation of lymphoma diagnosis based on pathology specimen review by panel of pathologists with expertise in hematologic malignancies. Specimens considered inadequate for 129 of 136 unconfirmed cases.
[e] Total exclusions less than sum of individual exclusions because multiple exclusion categories apply.

Table 3 Allergy history in relation to risk for NHL

Allergy history	Cases (n = 952)	Controls (n = 1691)	OR[a] (95% CI)
No	704	1215	1.0 reference
Yes	248	476	1.0 (0.8–1.2)
1 allergy	133	271	0.9 (0.7–1.2)
2 allergies	60	121	0.9 (0.6–1.2)
≥3 allergies	55	84	1.2 (0.9–1.8)
Plants[c]	141	258	1.0 (0.8–1.3)
Dust	84	166	0.9 (0.7–1.2)
Food	40	79	1.1 (0.7–1.6)
Animals	37	64	1.1 (0.7–1.7)
Medication	62	112	1.0 (0.7–1.4)
Insect bite or sting	8	13	1.1 (0.5–2.8)
Specific chemical[b]	11	8	2.7 (1.1–7.0)
Class of compound	5	20	0.5 (0.2–1.2)
Tobacco smoke	6	7	1.6 (0.5–4.8)
Fabrics	7	11	1.2 (0.4–3.1)

[a] ORs are adjusted for age, cancer registry, race/ethnicity, and education. All ORs are in reference to controls.
[b] Chemical allergies among cases include ammonia (n = 1), chromate (n = 1), diesel fumes (n = 1), kapok (n = 1), mercury (n = 1), pesticide (n = 1), sulfur (n = 3), and chemical not otherwise specified (n = 2); chemical allergies among controls include diesel fumes (n = 1), kapok (n = 1), pesticide (n = 2), sulfur (n = 1), textile chemical (n = 1), and chemical not otherwise specified (n = 2).
[c] Plant allergies include those to pollen, hay, grass, leaves, and molds.

pathology department where the case was diagnosed. An adequate tissue specimen was received, and a pathology review panel consensus diagnosis of NHL was made for 1,511 cases. Of 15,768 households contacted for screening to select potential controls, 14,328 (91.4%) provided information on eligibility (Table 2). Of 4,822 households with an eligible man, 4,381 households provided a name and address, and 2,299 were randomly selected for interview. Among selected men, 1,910 (83.1%) completed the interview. For this analysis, the study population was limited to living cases and controls. Study participants were further excluded if the interviewer considered the interview to be of poor quality or the interviewee to be uncooperative, if study participants had a history of AIDS or risk factors strongly associated with AIDS (history of injecting drug use and homosexual/bisexual orientation) or if medical history of allergy was incomplete. The final study population included 952 NHL cases and 1,691 controls.

Lymphoma classification was based on review of tissue specimens by a panel of pathologists with special expertise in diagnosis of hematological malignancies. NHL cases were classified into histopathological subtypes using a coding algorithm (26) that applies the International Classification of Diseases for Oncology (27) to the Working Formulation: [follicular: 9696, 9691, and 9642; diffuse: 9634, 9640, 9613, 9622, and 9624; small cell lymphocytic: 9611 and 9620; immunoblastic (including 5 lymphoblastic cases): 9602 and 9612; and other: 9591, 9600, 9621, 9694, and 9750].

Information was collected by trained interviewers who administered structured questionnaires by telephone. Study participants were classified as having a medical history of allergy based on the question, "Did a doctor ever tell you that you had allergies?" Those with a general history of allergy were queried about specific allergies and individual responses coded verbatim. Risks were assessed for NHL overall and stratified by subtype in relation to a general history of allergy and 10 specific types of allergies: plant (pollen, hay, grass, leaves, and molds), dust, food, animal, medication, insect sting or bite, specific chemical (including sulfur, chromate, formaldehyde, ammonia, mercury, kapok, diesel fumes, pesticide chemicals, and textile chemicals), classes of compounds (including soaps, detergents, perfumes, inks, paints, stains, oils, adhesives, metals, and food preservatives), tobacco smoke, and fabric. Allergies reported by <10 study participants were excluded from analyses if they could not be combined meaningfully into a larger group.

Statistical analyses were performed using SAS Software. Multivariate unconditional logistic regression was used to calculate ORs and 95% CIs. All analyses included adjustment for the matching variables of age (5-year date-of-birth intervals) and cancer registry, as well as the potential confounders of education (≤high school and >high school) and race/ethnicity (Caucasian, African-American, Hispanic, and other).

Results

A history of physician-diagnosed allergy was reported by 26% of NHL cases and 28% of controls (Table 3). Compared with men reporting no allergy history, men with a history of allergy had comparable risks for NHL overall (OR: 1.0; 95% CI: 0.8–1.2), follicular NHL (OR: 1.0; 95% CI: 0.7–1.3), and small cell lymphocytic NHL (OR: 1.0; 95% CI: 0.6–1.5). There was a nonsignificantly decreased risk for diffuse NHL (OR: 0.8; 95% CI: 0.6–1.1) and a nonsignificantly increased risk for immunoblastic NHL (OR: 1.4; 95% CI: 0.9–2.1). A chemical allergy was associated with a significantly increased overall risk for NHL (OR: 2.7; 95% CI: 1.1–7). No significant associations with overall NHL risk were found for other types of allergies.

Stratification by NHL subtype (Table 4) revealed that a chemical allergy was associated with a significantly increased risk for diffuse NHL (OR: 4.1; 95% CI: 1.5–11.3) and small cell lymphocytic NHL (OR: 7.3; 95% CI: 1.8–30.4). An allergy to insect bites or stings was associated with a significantly increased risk for immunoblastic NHL (OR: 5.1; 95% CI: 1.4–19.2).

Table 4 Allergy history in relation to risk for NHL subtypes

Allergy history	No.	Follicular (n = 269) OR[a] (95% CI)	No.	Diffuse (n = 408) OR[a] (95% CI)	No.	Small cell (n = 117) OR[a] (95% CI)	No.	Immunoblastic[b] (n = 113) OR[a] (95% CI)
No	199	1.0 reference	311	1.0 reference	87	1.0 reference	76	1.0 reference
Yes	70	1.0 (0.7–1.3)	97	0.8 (0.6–1.1)	30	1.0 (0.6–1.5)	37	1.4 (0.9–2.1)
1 allergy	41	1.0 (0.7–1.5)	48	0.7 (0.5–1.0)	15	0.8 (0.5–1.5)	24	1.6 (1.0–2.5)
2 allergies	15	0.8 (0.4–1.4)	22	0.7 (0.5–1.2)	8	1.0 (0.5–2.1)	9	1.3 (0.6–2.6)
≥3 allergies	14	1.1 (0.6–1.9)	27	1.4 (0.9–2.1)	7	1.3 (0.6–2.9)	4	0.9 (0.3–2.6)
Plants[c]	36	0.9 (0.6–1.4)	62	1.0 (0.7–1.4)	17	1.1 (0.6–1.9)	17	1.2 (0.7–2.1)
Dust	21	0.8 (0.5–1.3)	37	0.9 (0.6–1.3)	9	0.8 (0.4–1.6)	10	1.0 (0.5–2.1)
Food	12	1.1 (0.6–2.1)	19	1.1 (0.6–1.8)	2	0.5 (0.1–2.0)	6	1.5 (0.6–3.6)
Animals	15	1.5 (0.8–2.8)	12	0.8 (0.4–1.6)	5	1.4 (0.5–3.7)	2	0.7 (0.2–2.8)
Medication	21	1.2 (0.7–1.9)	18	0.6 (0.4–1.0)	10	1.1 (0.5–2.3)	11	1.7 (0.9–3.3)
Insect bite or sting	1	0.4 (0.1–3.3)	2	0.7 (0.2–3.4)	2	2.6 (0.5–12.7)	3	5.1 (1.4–19.2)
Specific chemical	0		8	4.1 (1.5–11.3)	3	7.3 (1.8–30.4)	0	
Class of compound	1	0.3 (0.0–2.1)	4	0.8 (0.3–2.3)	0		0	
Tobacco smoke	1	0.8 (0.1–6.7)	3	1.6 (0.4–6.4)	0		1	3.2 (0.4–28.0)
Fabrics	3	1.8 (0.5–6.9)	2	0.8 (0.2–3.8)	1	1.4 (0.2–12.5)	0	

[a] ORs are adjusted for age, cancer registry, race/ethnicity, and education. All ORs are in reference to controls.
[b] Cases of immunoblastic NHL (n = 108) and five cases of lymphoblastic NHL (n = 5). All cases with insect bite allergies were immunoblastic NHL.
[c] Plant allergies include those to pollen, hay, grass, leaves, and molds.

Discussion

In our study population, we found no evidence that a general history of allergy was associated with either a significantly increased or decreased risk for NHL. Similarly, no significant associations were evident for the most commonly reported specific allergies, including those to plants, dust, food, animals, and medications. Chemical allergies and insect bite allergies appeared to significantly increase risk for certain NHL subtypes. However, these allergies were reported infrequently and together accounted for only about 5% of study participants with allergies.

Consistent with our finding that a general allergy history is neither a risk factor nor a protective factor for NHL, 8 of 12 studies previously investigating the general association between allergy and NHL (13, 15–18, 20–22) did not find a statistically significant relationship. Of the remaining studies, 2 reported a significantly increased risk (11, 12), and 2 reported a significantly decreased risk (7, 8). In both studies reporting a significant increase in risk (11, 12) and one of the two reporting a significant decrease in risk (8), the associations were for NHL in combination with other lymphoproliferative malignancies. In the one study for which a significant decrease in risk was found for NHL alone (7), the study population was comprised of HIV-positive and HIV-negative homosexual men, among whom the strongest associations were found for the HIV-positive group. As HIV infection usually progresses to AIDS, and AIDS has been associated with a >100-fold increase in NHL risk (4), these latter findings cannot be generalized easily to other populations.

Associations between specific allergy types and risk for NHL have been examined in a prospective study (11) and four case control studies (6, 7, 9, 13). However, apart from two of the case control studies (6, 7), companion studies reported by the same investigators, there was little evidence for association. The prospective study (11) found no significant associations for allergies to medication, chemicals, bee stings, and poisonous plants. However, relative risks were all above one. In a hospital-based case control study, Cartwright *et al.* (13) found no significant associations for specific allergies, including those to food, pollen/dust, and medication. In a population-based case control study, Bernstein *et al.* (9) investigated NHL risk separately for men and women in relation to 15 different allergy groups, including pollen/dust, animals, insect bites/stings, and several categories of food. The only significant finding reported was a decreased risk for NHL, of borderline significance, among men with an allergy to nuts and berries. In companion population-based case control studies, Holly *et al.* (6, 7) investigated the relation of allergy to NHL among HIV-positive homosexual men, HIV-negative homosexual men, heterosexual men, and women. They found specific allergies to be variably associated with decreased risks for NHL in each group, but findings were inconsistent, and no specific allergy significantly decreased NHL risk across all four groups. The associations were weakest for heterosexual men, the group most comparable with our study population.

A review of the literature (Table 1) indicated some differences in associations for allergy-related conditions. Of several studies looking at NHL in relation to asthma (6, 10, 11, 16, 17) and hay fever (9, 11, 15, 19), no significant associations were found, although there was a suggestion of decreased risk as risk estimates were all less than or equal to one. In contrast, there was some evidence of increased NHL risk in four of five studies looking at associations with hives (6, 9, 10, 12). The most striking association was based on prospective data for lymphoma, leukemia, and myeloma combined, showing significantly increased relative risks of 7.9 for any history of physician-diagnosed hives and 9.3 for a 5-year history of hives (12). In case control studies of NHL, Fabbro-Peray *et al.* (10) found a significantly increased OR of 1.7, Bernstein and Ross (9) found an increased OR of 1.2 of borderline significance, and Holly *et al.* (6) found a nonsignificantly increased OR of 1.2 for heterosexual men, albeit a significantly decreased risk for women. Results from one prospective study could not be interpreted meaningfully because of limited sample sizes (17).

Our observation that chemical allergies increased risk for diffuse and small cell lymphocytic NHL is of interest in that many chemicals have been implicated as NHL risk factors (28), and for some of these chemicals, there is evidence that the increased risk may be specific to the diffuse and small cell lymphocytic subtypes (29, 30). The significantly increased risk for immunoblastic NHL among men with an allergy to insect bites or stings is novel. However, it is notable in the light of recent reports suggesting that hypersensitivity to mosquito bites is associated with an increased risk of malignant histiocytosis

(31, 32), most cases of which are now considered to be large cell immunoblastic lymphomas, as classified by the Working Formulation (33).

One of the major advantages of this study is that, in addition to a large study population from which data were collected on physician-diagnosed allergies, pathology specimens were obtained for nearly all study participants, and an NHL diagnosis was confirmed by a panel of pathologists with expertise in diagnosis of hematologic malignancies. To our knowledge, this is also the first study that has explored associations between specific allergies and risk for NHL subtypes. However, several methodological limitations need to be kept in mind.

First, chance may explain some or all of the significant associations found for allergies to chemicals and insect bites in relation to increased risk for NHL. The potential for chance associations may have been increased by the many allergy-specific comparisons across strata for NHL subtypes. Also, CIs around the estimates of increased NHL risk for chemical and insect allergies were quite wide, as these allergies were reported relatively infrequently. At the same time, the associations were strong, and the lower bounds of the CIs were all well above one. Therefore, the possibility that allergies to chemicals and insect bites are true risk factors for NHL would appear to merit further investigation.

Second, selection bias could have arisen in the process of recruiting cases and controls for study participation. This possibility was minimized, however, through identification of cases from population-based cancer registries and the use of random-digit dialing to randomly select controls from corresponding geographic regions. The validity of random-digit dialing to generate a population-based sample has been well documented for the time period during which the Selected Cancers Study was conducted (34). Moreover, participation rates for both cases and controls were high. Selection bias could also have been introduced by application of exclusionary criteria to define the subpopulation of confirmed NHL cases and frequency-matched controls for analysis. The two major exclusionary criteria were proxy interviews and a history of AIDS. Proxy interviews were excluded based on previous Selected Cancers Study findings (35) showing that they compromised internal validity, although our findings conceivably might have been affected by exclusion if allergy was associated very strongly with survival after NHL diagnosis. This could have resulted in underestimation of subtype-specific increases in NHL risk found for chemical and insect allergies, as these subtypes have a relatively poor prognosis. Because of the overwhelming association between AIDS and NHL (290 cases and 1 control in our study population), it would not have been possible to adjust for confounding. As a consequence, however, our findings cannot be generalized to men with AIDS or AIDS risk factors of homosexual/bisexual orientation and injecting drug use.

Third, differential misclassification of cases and controls on exposure status may have influenced our findings for several reasons. Recall bias could have resulted from an increased likelihood of cases to remember having an allergy compared with controls, although the lack of any significant associations for a general history of allergy, or for the most commonly reported specific allergies, suggests that this is unlikely. Interviewer bias could have resulted from systematic differences in interviewing styles between cases and controls, albeit unlikely as the data were originally collected to address unrelated hypotheses. Because we did not specifically ask study participants when they were diagnosed with an allergy, a temporal bias may have occurred if, for some cases, allergy developed as a result of cancer. However, this is unlikely as existing data suggest that NHL is associated with remission of allergy symptoms rather than exacerbation of preexisting allergies or development of new allergies (22). Detection bias could also account for an apparent association between allergy and NHL if allergies resulted in more frequent contact with health care providers and an increased likelihood of diagnosis with NHL. This is also unlikely, however, as screening for NHL is uncommon.

In summary, we found no evidence for an association between a general history of allergy and NHL in our study population of heterosexual men. Similarly, we found no significant associations for commonly reported specific allergies, which were to plants, dust, food, animals, and medications. There was some suggestion that an insect bite allergy increased risk for immunoblastic NHL, and an allergy to chemicals increased risks for small cell lymphocytic NHL and diffuse NHL. These latter findings have not been reported previously. However, as we did not investigate allergy-specific associations based on *a priori* hypotheses, they will need to be confirmed by other studies.

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