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Population-based Study of Non-Hodgkin Lymphoma, Histology, and Medical History among Human Immunodeficiency Virus-negative Participants in San Francisco

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A population-based case-control study of non-Hodgkin lymphoma was conducted in the San Francisco Bay Area of California from 1988 to 1995. The study used Working Formulation histologic subtypes of non-Hodgkin lymphoma. Diffuse and immunoblastic large-cell lymphomas and all follicular lymphomas were combined to reflect two Revised European-American Lymphoma (REAL) classifications. Results were obtained from age- and sex-adjusted polytomous multivariable logistic models for 1,304 cases and 2,402 controls who were negative for human immunodeficiency virus. Statistically significant odds ratios for REAL large-cell lymphoma were decreased for receipt of five or more different vaccines (odds ratio (OR) = 0.65), use of calcium channel blockers (OR = 0.35), mononucleosis (OR = 0.55), plant allergies (OR = 0.72), and animal allergies (OR = 0.40). Odds ratios for REAL follicular lymphoma were decreased for use of nonsteroidal antiinflammatory drugs (OR = 0.67), hepatitis (OR = 0.36), and having had three or more bee or wasp stings (OR = 0.79) and were increased for heart disease (OR = 1.5). Similar elevated odds ratios for heart disease and Bacillus Calmette-Guérin vaccine and decreased odds ratios for nonsteroidal antiinflammatory drugs, plant allergies, and three or more bee or wasp stings were found for small lymphocytic lymphoma. These data provide direction for further investigation of immune function and genetic characteristics of subtypes of non-Hodgkin lymphoma in lymphomagenesis and warrant analyses in large pooled data sets.

case-control studies; hypersensitivity; infection; lymphoma, non-Hodgkin; neoplasms by histologic type; risk factors; vaccines

Abbreviations: BCG, Bacillus Calmette-Guérin; HIV, human immunodeficiency virus; NHL, non-Hodgkin lymphoma; NSAIDs, nonsteroidal antiinflammatory drugs; REAL, Revised European-American Lymphoma; Th1, T helper type 1; Th2, T helper type 2.

Incidence rates for non-Hodgkin lymphoma (NHL) have increased since at least the 1930s (1, 2). Data from the Surveillance, Epidemiology, and End Results Program show that incidence rates for NHL increased at 4 percent per year for men and 3 percent per year for women from the early 1970s to 1990 for all racial groups combined, although data collected during the 1990s indicated that these increases may be diminishing for some groups (3, 4). Similar increases in age-adjusted NHL incidence and mortality rates have occurred worldwide, and while some of the increase has been attributed to infection with human immunodeficiency virus (HIV), most of it remains unexplained (5). Fewer risk factors have been identified by histologic subtype, and these studies have usually used subtype classifications developed prior to the newer Revised European-American Lymphoma (REAL) and World Health Organization subtype classifications.

Acquired and autoimmune conditions comprise the majority of established risk factors for all NHL subtypes combined. Autoimmune diseases that occur early in life do not appear to be associated with risk of NHL, whereas both exogenous (viral) and endogenous (autoantigens) conditions that result in sustained antigen drive are related to lymphomagenesis (6). These conclusions are consistent with studies showing that risk factors for lymphoproliferative disorders vary for early and late posttransplant disease among persons who have received immunosuppressive medications to prevent organ rejection (7, 8). Epidemiologic investigations

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also have reported increased risk of NHL with other types of severe immune suppression, including those associated with HIV infection (9), Sjögren's syndrome (10), and several rare genetic syndromes (11) and with Epstein-Barr virus and human T-cell lymphotropic virus type I in regions where these viruses are endemic (12, 13).

It is plausible that other immunity-altering factors, including medical history factors, may play a role in risk of NHL. Results from analyses of all types of NHL and subtypes of NHL have shown inconsistent associations with history of allergies (14–16). Elevated risks of low-grade lymphoma have been reported for hepatitis C virus infection (17), diabetes mellitus, use of diabetes drugs, and other cancers (18). High-grade lymphomas have been associated with antihistamine use and eczema. Gastric maltomas have been associated with *Helicobacter pylori* infection (19) and peptic ulcers (20), whereas B-cell chronic lymphocytic leukemia/lymphoma and high-grade extranodal lymphomas have been associated with blood transfusions (21), although overall blood transfusions do not appear to play a role (22).

We conducted a population-based case-control study of NHL in the San Francisco Bay Area of California between 1988 and 1995 to determine risk factors for all types of NHL combined and histologic subtypes of NHL. Results have been reported for HIV-related NHL (23–25) and non-HIV-related NHL (15, 22, 26–29). Evidence of fundamental differences by NHL histologic subtype has come from molecular studies that reported different genetic mutations by specific histologic subtype (30, 31) and clinical studies that reported differences in prognosis and response to treatment by subtype (32). Motivated in part by these data and earlier data, we hypothesized that some risk factors would vary by histologic subtype. We report here the associations for exposures related to medical history by histologic subtype, especially exposures that were important in our earlier analyses of all NHL, including decreased risks associated with allergies to plants, an increased number of bee and wasp stings, vaccine history, use of nonsteroidal antiinflammatory drugs (NSAIDs), and use of cholesterol-lowering drugs and increased risk associated with histamine-2 receptor antagonists (15, 24). These preliminary data may provide information for generating hypotheses about the etiology of NHL, as well as directions for future investigations.

MATERIALS AND METHODS

Study population

Rapid case ascertainment by the Northern California Cancer Center was used to identify NHL patients. Details have been published elsewhere (15, 24). Briefly, 593 patients (21 percent) died before they could be contacted, 275 (10 percent) were too ill for interview, 78 (3 percent) had physician-reported medical contraindications, 182 (6 percent) refused, 74 (3 percent) could not be located, and 17 (<1 percent) were unavailable for other reasons. HIV-positive patients and a smaller number of persons over 55 years of age with high-grade NHL comprised the majority of nonparticipating cases (27). A total of 1,593 NHL patients completed in-person interviews after human subjects approval and provision of informed consent. A total of 1,304 HIV-negative patients were included in these analyses. Random digit dialing (33–35) was used to identify control subjects. Random sampling of Health Care Financing Administration files was used for participants aged ≥65 years. Controls were frequency-matched to patients by age (within 5 years), sex, and county of residence (24). A total of 2,515 (78 percent) eligible control participants completed interviews, and 2,402 HIV-negative persons were included in these analyses.

Histologic subtype and grade were provided by the diagnosing pathologists, with additional review for 97 percent of all cases being conducted by Dr. Ronald F. Dorfman at Stanford University, who provided grade and subtype classification using the Working Formulation (36). If inadequate material was available for review, patients were classified as having NHL not otherwise specified. Since this study was conducted, the REAL and World Health Organization classifications for NHL subtypes have been implemented. Therefore, NHL follicular subtypes were combined into one category and the diffuse large-cell and immunoblastic large-cell subtypes were combined into another group to reflect the REAL classification (37–39) (hereafter called REAL follicular lymphoma and REAL large-cell lymphoma). The other Working Formulation subtypes were not regrouped because we had no immunohistochemistry results.

Statistical analysis

Statistical analyses were conducted using SAS software, version 8 (SAS Institute, Inc., Cary, North Carolina). Diseases and conditions (most of them physician-diagnosed) and use of medications were reported for events that had occurred more than 1 year prior to diagnosis (for cases) or interview (for controls). Reported medications had to have been used for 4 or more consecutive weeks. Medical history information included age at first and last use or at occurrence and number of years of use or number of episodes. Questions on the use of some medications were asked independently of questions about indications for use. Questions about drugs used to control epilepsy, seizures, gout, ulcers, weight, high blood cholesterol, or high blood pressure, antihistamines used for allergies, and cancer chemotherapy drugs were asked in conjunction with questions on the condition of interest. Information about drugs regularly received by injection alone was collected separately from information on oral and inhalation use.

The year in which participants received their hepatitis vaccinations was used to create categories for persons who were likely to have received only gamma globulin (before 1982) and persons who could have received either gamma globulin or hepatitis B vaccine (1982 or later). A dichotomous variable was created to represent the total lifetime number (<5 or ≥5) of different vaccines received, with diphtheria-pertussis-tetanus counted as one vaccine (15, 24). To evaluate possible exposure to poliomyelitis vaccine contaminated with simian virus 40, participants who had received polio vaccine between 1955 and 1963 were analyzed separately. A dichotomous variable, grouped

TABLE 1. Working Formulation* classification of histologic subtype for non-Hodgkin lymphoma patients, by sex, San Francisco Bay Area, California, 1988–1995†

Working Formulation classification subtype	Total (*n* = 1,304)		Men (*n* = 725)		Women (*n* = 579)	
	No.	%	No.	%	No.	%
Low grade	432	33	229	32	203	35
Small lymphocytic	152	12	79	11	73	13
Follicular small	140	11	68	9	72	12
Follicular mixed	108	8	60	8	48	8
Intermediate grade	697	53	381	53	316	55
Follicular large	104	8	51	7	53	9
Diffuse small	68	5	46	6	22	4
Diffuse mixed	75	6	42	6	33	6
Diffuse large	451	35	242	33	209	36
High grade	100	8	69	10	31	5
Immunoblastic	59	4.5	37	5	22	4
Lymphoblastic	12	1	9	1	3	0.5
Burkitt's, Burkitt's-like	28	2	22	3	6	1
Miscellaneous						
Mycosis fungoides	47	4	29	4	18	3
Not otherwise specified	60	5	40	5.5	20	3

* Created by the Non-Hodgkin's Lymphoma Classification Project (36).

† Not all lymphomas that were graded using the Working Formulation could be assigned a Working Formulation histologic subtype, and one woman with a diffuse mixed subtype could not be graded; thus, numbers may not add up to the totals for groupings by grade. Only men and women who were negative for human immunodeficiency virus were included.

according to the distribution among controls, was created to evaluate the total number of different self-reported major bacterial and viral infections.

Estimates of relative risk were computed as odds ratios and associated 95 percent confidence intervals using sex- and age-adjusted polytomous analyses. Risk factors were first evaluated independently. Based on results from the initial analyses, stepwise procedures were used to develop age- and sex-adjusted parsimonious polytomous models for small lymphocytic (REAL lymphoplasmacytic and lymphoplasmacytoid), REAL follicular, diffuse small cleaved-cell (REAL mantle-cell and marginal zone), diffuse mixed-cell (multiple REAL subtypes), and REAL large-cell lymphomas. Selection criteria for model variables were a p value less than or equal to 0.20 and the existence of five or more exposed patients. The inclusion criterion for model variables was a p value less than or equal to 0.10. Potential confounding factors were included if they altered risk estimates by more than 10 percent. All statistical tests were two-sided. Results for fewer than four NHL cases in a cell are not presented in the text, although some results are provided in the tables. Results for lymphoblastic and Burkitt's group lymphoma are not presented because of sparse data.

RESULTS

As in other industrialized western nations, follicular and diffuse large-cell lymphomas comprised the majority of NHL cases among these HIV-negative patients (table 1). Proportions were similar by sex, with the exception of a greater proportion of Burkitt's-like lymphoma in men.

Vaccinations

Most immunizations against infectious diseases were associated with a reduced risk of lymphoma, and associations varied by subtype (table 2). Bacillus Calmette-Guérin (BCG) vaccine was associated with increased risks for all subtypes, although many of the risk estimates were imprecise. Similar to results for all types of NHL (21), having received five or more vaccines was associated with a reduced risk of most subtypes.

Over-the-counter and prescription medications

Based on a priori hypotheses, questions on the use of many medications were asked directly and in association with specific diseases or conditions (table 3). The estimates based on more than three exposed cases were relatively consistent, with the exception of use of noninsulin medications for diabetes. More than two thirds of persons with adult-onset diabetes used noninsulin medications. Adjustment for body mass index as a measure of obesity, a risk factor for adult-onset diabetes, did not modify the observed effects with use of noninsulin diabetes medication. Risk estimates by subtype were elevated for users of cimetidine and another histamine-

TABLE 2. Odds ratios for non-Hodgkin lymphoma according to vaccine history, by Working Formulation* classification histologic subtype and two Revised European-American Lymphoma classification subtypes, among men and women who were negative for human immunodeficiency virus, San Francisco Bay Area, California, 1988–1995

Vaccine†	Working Formulation and ad hoc REAL‡ classification subtypes															No. of controls (*n* = 2,402)
	Small lymphocytic (*n* = 152)			REAL follicular (FSC, FM, FL)‡ (*n* = 352)			Diffuse small cleaved-cell (*n* = 68)			Diffuse mixed small cleaved and large-cell (*n* = 75)			REAL diffuse large-cell (DL, IBL)‡ (*n* = 510)			
	No.	OR‡,§	95% CI‡	No.	OR§	95% CI	No.	OR§	95% CI	No.	OR§	95% CI	No.	OR§	95% CI	
Diphtheria-pertussis-tetanus	75	0.83	0.56, 1.2	200	1.0	0.77, 1.3	35	0.96	0.54, 1.7	30	0.44	0.26, 0.73	271	0.85	0.68, 1.1	1,370
Measles	34	0.98	0.64, 1.5	90	0.91	0.69, 1.2	11	0.50	0.25, 0.99	13	0.57	0.30, 1.1	147	0.97	0.77, 1.2	778
Influenza	85	1.1	0.81, 1.6	168	0.92	0.72, 1.2	29	0.64	0.39, 1.1	30	0.65	0.40, 1.1	223	0.76	0.62, 0.93	1,152
Tetanus	127	0.66	0.41, 1.0	317	1.2	0.79, 1.8	60	0.81	0.38, 1.7	63	0.71	0.36, 1.4	418	0.56	0.43, 0.75	2,155
Tetanus for injury	87	0.82	0.58, 1.2	225	1.1	0.83, 1.4	44	1.0	0.60, 1.7	42	0.74	0.46, 1.2	292	0.76	0.62, 0.93	1,586
Smallpox	104	0.74	0.50, 1.1	253	0.91	0.68, 1.2	48	0.80	0.44, 1.5	48	0.61	0.36, 1.0	362	0.78	0.61, 0.99	1,788
Cholera	36	0.93	0.62, 1.4	74	0.84	0.63, 1.1	12	0.55	0.29, 1.1	15	0.69	0.38, 1.2	94	0.65	0.51, 0.84	642
Yellow fever	32	1.1	0.71, 1.7	58	0.86	0.63, 1.2	11	0.66	0.33, 1.3	10	0.56	0.28, 1.1	76	0.67	0.51, 0.89	514
Typhoid	4	0.63	0.22, 1.8	12	0.91	0.49, 1.7				4	1.4	0.49, 3.9	10	0.51	0.26, 0.99	89
Bacillus Calmette-Guérin	6	2.8	1.2, 6.8	7	1.2	0.54, 2.7				2	1.7	0.40, 7.2	13	1.6	0.84, 3.0	41
Poliomyelitis¶	95	0.68	0.46, 0.99	257	0.97	0.73, 1.3	47	0.71	0.41, 1.2	46	0.69	0.39, 1.2	354	0.82	0.64, 1.0	1,836
>1963	9	0.38	0.18, 0.79	32	0.67	0.42, 1.0	7	0.61	0.25, 1.5	10	0.85	0.38, 1.9	63	0.80	0.56, 1.1	350
≤1963	65	0.72	0.48, 1.1	179	1.0	0.78, 1.4	26	0.60	0.33, 1.1	28	0.66	0.36, 1.2	227	0.81	0.63, 1.0	1,197
Age ≥10 years	62	0.65	0.43, 0.97	174	1.0	0.75, 1.4	31	0.65	0.37, 1.2	221	0.70	0.39, 1.3	221	0.82	0.63, 1.0	1,054
Age <10 years	12	0.90	0.37, 2.2	38	0.58	0.35, 0.98	3	0.20	0.05, 0.83	65	0.73	0.25, 2.2	65	0.69	0.45, 1.1	505
Hepatitis#	19	0.85	0.51, 1.4	43	0.74	0.53, 1.0	9	0.94	0.46, 1.9	6	0.47	0.20, 1.1	53	0.61	0.45, 0.83	389
<1982	15	0.98	0.56, 1.7	29	0.74	0.50, 1.1	7	1.1	0.48, 2.4	4	0.47	0.17, 1.3	35	0.60	0.41, 0.87	259
≥1982	3	0.44	0.14, 1.4	14	0.75	0.43, 1.3				2	0.50	0.12, 2.1	16	0.57	0.34, 0.98	127
≥5 (vs. <5) different vaccines**	91	0.72	0.51, 1.0	235	0.88	0.69, 1.1	42	0.72	0.44, 1.2	39	0.48	0.30, 0.76	300	0.61	0.50, 0.75	1,718

* Developed by the Non-Hodgkin's Lymphoma Classification Project (36).
† The referent group for each vaccine comprised participants who reported never having received that specific vaccine.
‡ REAL, Revised European-American Lymphoma; FSC, follicular small cleaved-cell; FM, follicular mixed small cleaved and diffuse-cell; FL, follicular large-cell; DL, diffuse large-cell; IBL, immunoblastic large-cell; OR, odds ratio; CI, confidence interval.
§ Age- and sex-adjusted odds ratios from polytomous models for human immunodeficiency virus-negative women and men combined. Empty cells indicate that estimates were not computed because there were no exposed participants or only one exposed participant in that cell.
¶ The referent group for poliomyelitis analyses was those not immunized against poliomyelitis. Persons immunized in 1963 or earlier were more likely to have been exposed to vaccine contaminated with simian virus 40.
# Hepatitis vaccines received prior to 1982 were immunoglobulin vaccines.
** Diphtheria-pertussis-tetanus was counted as one vaccine.

2 receptor antagonist, whereas decreased risk estimates were observed for cholesterol-lowering drugs. Use of calcium channel blockers and beta-blockers was reported separately from use of these drugs for high blood pressure by persons who used them for purposes other than control of high blood pressure. Unlike the nonsignificant, slightly elevated risks for high blood pressure drugs, beta-blockers were associated with a larger increased risk of REAL follicular lymphoma and calcium channel blockers were associated with a decreased risk of REAL large-cell lymphoma. Use of steroids, antihistamines, and allergy and asthma drugs tended to show decreased risks despite various routes of administration. Use of NSAIDs showed a pattern of decreased risk, in contrast to the elevated risk for parenteral pain and antiarthritis drugs that included gold and other miscellaneous treatments.

Diseases and conditions that occurred 5 or more years prior to diagnosis

Results were grouped under three broad categories: infectious diseases, chronic diseases, and allergies (table 4). Relatively consistently decreased risk estimates were found for REAL large-cell lymphoma in association with history of infectious diseases. There also were decreased risk estimates for REAL follicular lymphoma associated with history of hepatitis and infectious mononucleosis. Elevated risk estimates for low-grade lymphomas classified as small lymphocytic and REAL follicular were apparent for heart disease and ulcers. Risk estimates for the intermediate to high-grade lymphomas tended to be near unity or below unity, with the exception of increased risks with diabetes mellitus (diffuse mixed) and endocrine gland disorders (REAL large-cell). Risk estimates below unity were evident for three subtypes associated with previous cancers and for REAL large-cell lymphomas associated with blood disorders. Decreased estimated risks were observed for allergies and allergic conditions by subtype, with the exception of hives and childhood eczema.

Multivariable models

In multivariable analyses, BCG vaccine was associated with increased risk of two subtypes, whereas diphtheria-pertussis-tetanus, hepatitis, and measles vaccines were each associated with reduced risk (table 5). Having had five or

TABLE 3. Odds ratios for non-Hodgkin lymphoma according to use of medication for 4 or more consecutive weeks, by Working Formulation* classification histologic subtype and two Revised European-American Lymphoma classification subtypes, among men and women who were negative for human immunodeficiency virus, San Francisco Bay Area, California, 1988–1995

Medication	Working Formulation and ad hoc REAL† classification subtypes															No. of controls (*n* = 2,402)
	Small lymphocytic (*n* = 152)			REAL follicular (FSC, FM, FL)† (*n* = 352)			Diffuse small cleaved-cell (*n* = 68)			Diffuse mixed small cleaved and large-cell (*n* = 75)			REAL diffuse large-cell (DL, IBL)† (*n* = 510)			
	No.	OR†,‡	95% CI†	No.	OR‡	95% CI	No.	OR‡	95% CI	No.	OR‡	95% CI	No.	OR‡	95% CI	
Dilantin				9	1.9	0.90, 4.0				2	2.0	0.48, 8.7	4	0.57	0.20, 1.6	34
Cimetidine plus§	5	4.0	1.5, 11	4	1.3	0.46, 4.0							11	2.4	1.2, 5.1	21
Noninsulin drugs for diabetes	8	1.3	0.62, 2.8	4	0.33	0.12, 0.91	3	1.1	0.34, 3.6	7	2.8	1.2, 6.4	21	1.3	0.76, 2.1	70
Cholesterol-lowering drugs	4	0.44	0.16, 1.2	12	0.69	0.37, 1.3	4	1.1	0.38, 3.1	2	0.50	0.12, 2.1	15	0.60	0.34, 1.0	100
High blood pressure drugs¶	44	1.1	0.78, 1.7	89	1.2	0.93, 1.6	15	0.84	0.46, 1.5	20	1.2	0.70, 2.1	126	1.2	0.96, 1.6	445
Calcium channel blockers#	5	0.73	0.29, 1.8	7	0.55	0.25, 1.2							7	0.38	0.17, 0.84	72
Beta-blockers#	2	1.4	0.31, 6.4	7	2.9	1.1, 7.4							3	0.87	0.24, 3.1	13
Steroids**	10	0.85	0.44, 1.6	23	0.82	0.52, 1.3	7	1.4	0.64, 3.2	7	1.2	0.56, 2.7	33	0.81	0.55, 1.2	187
Antihistamines††	11	0.55	0.29, 1.0	37	0.76	0.53, 1.1	6	0.73	0.31, 1.7	11	1.2	0.61, 2.2	56	0.80	0.59, 1.1	320
Nonsteroidal antiinflammatory drugs	9	0.36	0.18, 0.73	32	0.70	0.47, 1.0	9	0.94	0.46, 1.9	4	0.37	0.13, 1.0	52	0.81	0.59, 1.1	263
Sulfonamides plus‡‡				2	0.69	0.16, 3.0	3	5.1	1.5, 18				10	2.4	1.1, 5.1	20
Diazepam	14	1.2	0.66, 2.1	18	1.5	0.93, 2.5	3	0.61	0.19, 2.0	3	0.51	0.16, 1.6	27	0.69	0.45, 1.1	163
Antidepressants	3	0.63	0.19, 2.0	10	0.82	0.42, 1.6	2	1.0	0.25, 4.3	3	1.2	0.38, 4.1	9	0.51	0.25, 1.0	81
Drugs received by injection§§																
Allergy/asthma drugs not otherwise specified	2	0.19	0.05, 0.78	15	0.61	0.35, 1.0	2	0.43	0.10, 1.8	5	0.99	0.39, 2.5	20	0.55	0.34, 0.89	171
Miscellaneous antiarthritis drugs¶¶/painkillers				4	5.4	1.4, 21							3	2.8	0.66, 12	5
Iron				6	3.0	1.1, 8.3							4	1.4	0.45, 4.6	10

* Developed by the Non-Hodgkin's Lymphoma Classification Project (36).
† REAL, Revised European-American Lymphoma; FSC, follicular small cleaved-cell; FM, follicular mixed small cleaved and diffuse-cell; FL, follicular large-cell; DL, diffuse large-cell; IBL, immunoblastic large-cell; OR, odds ratio; CI, confidence interval.
‡ Age- and sex-adjusted odds ratios from polytomous models for human immunodeficiency virus-negative women and men combined. Empty cells indicate that estimates were not computed because there were no exposed participants or only one exposed participant in that cell.
§ Cimetidine and another histamine-2 receptor antagonist.
¶ High blood pressure drugs included diuretics, reserpine, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, methyldopa, guanfacine, guanabenz, prazosin, and hydralazine.
# Calcium channel blockers and beta-blockers were reported under other drugs taken and were not reported when participants were asked about drugs used to control high blood pressure.
** Excludes steroids received by injection only (among all users, 72% were oral and 16% were creams).
†† Antihistamines included only those medications marketed primarily as antihistamines.
‡‡ Sulfonamides and other antibacterial agents.
§§ From responses to an open-ended question regarding medication regularly received by injection alone.
¶¶ Miscellaneous shots for arthritis included gold.

more different vaccinations was associated with decreased risk of REAL large-cell lymphoma. Among medications, NSAID use was associated with a reduced risk, whereas use of cimetidine and another histamine-2 receptor antagonist was associated with a substantially increased risk. Use of noninsulin medications for diabetes mellitus was associated with a nearly threefold increased risk of one subtype and a 70 percent decreased risk of another. Beta-blockers were associated with REAL follicular lymphoma; calcium channel blockers and sulfonamides and other antibacterial agents were associated with REAL large-cell lymphoma. Heart disease was the only disease associated with an increased risk of more than one subtype. Other diseases and conditions were uniquely associated with risk of different subtypes. Childhood eczema was associated with an increased risk of REAL large-cell lymphoma. Allergies and total number of bee or wasp stings were associated with reduced risk of two subtypes.

DISCUSSION

These results support a role for personal medical history in the etiology of NHL subtypes beyond the established immunosuppressive diseases and conditions (9–11). The medical history factors we investigated have the potential to modify immune system function, and these factors may vary by NHL subtype.

Our results were based on self-reported medical history, not medical records. Using medical records to collect information does not guarantee that the estimated prevalence of a condition is more reliable than that based on self-report (40). Only information that pertains to diseases and conditions that require medical attention in a hospital or a physician's office is likely to be recorded in a medical record. Medical records are likely to be incomplete for minor conditions, for conditions with no medical visit or a visit that occurred in the distant past, and for persons who have received care from multiple facilities. Therefore, in-person interviews provide a better estimate of the prevalence of many medical conditions

TABLE 4. Odds ratios for non-Hodgkin lymphoma according to the presence of diseases and conditions diagnosed 5 or more years prior to diagnosis (cases) or interview (controls), by Working Formulation* classification histologic subtype and two Revised European-American Lymphoma classification subtypes, among men and women who were negative for human immunodeficiency virus, San Francisco Bay Area, California, 1988–1995

Disease or condition	Working Formulation and ad hoc REAL† classification subtypes															No. of controls (*n* = 2,402)
	Small lymphocytic (*n* = 152)			REAL follicular (FSC, FM, FL)† (*n* = 352)			Diffuse small cleaved-cell (*n* = 68)			Diffuse mixed small cleaved and large-cell (*n* = 75)			REAL diffuse large-cell (DL, IBL)† (*n* = 510)			
	No.	OR†,‡	95% CI†	No.	OR‡	95% CI	No.	OR‡	95% CI	No.	OR‡	95% CI	No.	OR‡	95% CI	
Infectious diseases/conditions																
Parasitic infections	11	0.85	0.45, 1.6	35	1.1	0.76, 1.6	3	0.52	0.16, 1.7	3	0.46	0.14, 1.5	31	0.66	0.44, 0.97	218
Tooth abscess	41	0.74	0.50, 1.1	105	1.2	0.89, 1.5	17	0.94	0.53, 1.7	17	0.84	0.48, 1.5	111	0.77	0.61, 0.98	588
Fever blisters	39	0.78	0.53, 1.1	114	1.2	0.90, 1.5	20	0.93	0.54, 1.6	21	0.88	0.52, 1.5	120	0.71	0.56, 0.89	704
Canker sores	35	0.86	0.58, 1.3	85	0.84	0.64, 1.1	11	0.62	0.32, 1.2	13	0.55	0.30, 1.0	114	0.74	0.58, 0.93	678
Hepatitis	6	0.61	0.26, 1.4	9	0.38	0.19, 0.75	2	0.42	0.10, 1.7	6	1.2	0.52, 2.9	23	0.68	0.44, 1.1	165
Mononucleosis	9	1.0	0.52, 2.1	16	0.60	0.35, 1.0	4	0.98	0.35, 2.8	5	0.98	0.39, 2.5	23	0.58	0.37, 0.91	196
Pneumonia or other lung infection	41	1.4	0.95, 2.0	84	1.2	0.88, 1.5	16	1.2	0.65, 2.1	12	0.71	0.38, 1.3	97	0.88	0.69, 1.1	495
Shingles	16	1.7	0.97, 3.0	20	0.99	0.60, 1.6	3	0.72	0.22, 2.3				28	0.96	0.62, 1.5	120
Frequent infections	11	0.58	0.31, 1.1	52	1.2	0.89, 1.7	2	0.27	0.07, 1.1	9	1.0	0.50, 2.1	46	0.73	0.52, 1.0	258
>3 (vs. ≤3) different viral infections§	58	0.96	0.68, 1.4	128	0.90	0.71, 1.1	25	0.95	0.57, 1.6	30	1.0	0.65, 1.7	156	0.67	0.55, 0.83	941
≥2 (vs. 0) different bacterial infections¶	50	1.2	0.74, 1.8	108	1.1	0.83, 1.5	24	1.3	0.68, 2.5	21	0.71	0.39, 1.3	123	0.72	0.55, 0.94	674
Chronic diseases/conditions																
Heart disease	28	1.6	1.0, 2.5	50	1.4	0.99, 1.9	8	0.88	0.41, 1.9	6	0.66	0.28, 1.5	56	1.0	0.75, 1.4	233
Duodenal/peptic ulcer	25	1.7	1.1, 2.7	38	1.2	0.82, 1.7	9	1.2	0.61, 2.6	7	0.94	0.42, 2.1	49	1.0	0.74, 1.4	213
Diabetes mellitus	8	1.3	0.61, 2.8	11	0.87	0.45, 1.7				8	3.1	1.4, 6.7	20	1.1	0.68, 1.9	74
Previous "other" cancer#	22	1.1	0.67, 1.8	27	0.66	0.43, 1.0	8	0.99	0.45, 2.1	2	0.19	0.05, 0.78	37	0.63	0.43, 0.91	211
Endocrine gland disorders				2	0.89	0.20, 3.9							9	2.8	1.2, 6.5	15
Blood disorders	13	0.82	0.44, 1.5	43	1.2	0.80, 1.7	5	0.94	0.36, 2.4	8	0.93	0.41, 2.1	38	0.68	0.47, 0.99	207
Rheumatoid arthritis	5	1.2	0.45, 3.0	14	1.6	0.86, 3.0							15	1.2	0.68, 2.2	47
Nonrheumatoid arthritis	37	1.4	0.92, 2.1	58	1.0	0.75, 1.4	5	0.36	0.14, 0.93	14	1.2	0.63, 2.2	74	0.91	0.68, 1.2	300
Tonsillectomy	89	1.1	0.80, 1.6	207	1.2	0.98, 1.6	39	1.2	0.71, 1.9	37	0.82	0.51, 1.3	243	0.78	0.64, 0.95	1,228
Allergies and allergic conditions																
Animal dander	5	0.58	0.23, 1.4	18	0.72	0.43, 1.2	2	0.52	0.12, 2.2	5	1.0	0.41, 2.7	13	0.34	0.19, 0.61	179
Plants, etc.**	23	0.51	0.33, 0.81	87	0.85	0.66, 1.1	18	1.0	0.61, 1.8	24	1.3	0.78, 2.1	100	0.63	0.50, 0.80	691
Unknown allergies with hives	9	2.2	1.1, 4.5	20	2.1	1.3, 3.6	3	1.7	0.51, 5.5	4	2.0	0.71, 5.7	23	1.7	1.0, 2.8	62
Childhood eczema				12	0.94	0.51, 1.8	2	0.96	0.23, 4.0	2	0.78	0.19, 3.2	29	1.6	1.1, 2.6	81
Other factors																
≥3 bee or wasp stings	44	0.58	0.40, 0.84	129	0.81	0.64, 1.0	24	0.71	0.42, 1.2	24	0.64	0.38, 1.0	187	0.79	0.64, 0.97	1,066

* Developed by the Non-Hodgkin's Lymphoma Classification Project (36).

† REAL, Revised European-American Lymphoma; FSC, follicular small cleaved-cell; FM, follicular mixed small cleaved and diffuse-cell; FL, follicular large-cell; DL, diffuse large-cell; IBL, immunoblastic large-cell; OR, odds ratio; CI, confidence interval.

‡ Age- and sex-adjusted odds ratios from polytomous models for human immunodeficiency virus-negative women and men combined. Empty cells indicate that estimates were not computed because there were no exposed participants or only one exposed participant in that cell.

§ Viral infections included measles, mumps, chickenpox, rubella, hepatitis, shingles, poliomyelitis, infectious mononucleosis, herpes, genital herpes, and genital warts.

¶ Bacterial infections included scarlet fever, rheumatic fever, pertussis, tuberculosis, pneumonia, tooth abscess, gonorrhea, syphilis, and miscellaneous other bacterial infections.

A total of 107 cases and 211 control participants reported other cancers, including nonmelanoma skin cancer, melanoma, breast cancer, reproductive cancer, colon cancer, thyroid cancer, and multiple types. Skin and breast cancers comprised approximately 70% of reported other cancers.

** Grass, trees, pollen, ragweed, hay fever, seasonal allergies, etc.

in the general population. Finally, unless the condition was known by the patient to be associated with his or her lymphoma, recall of medical history would not be expected to differ between cases and controls. Information on the reason for use of some medications was not obtained, which limited our ability to evaluate the internal consistency and validity of data pertaining to medication use and diseases. Given the number of exposures investigated, it also is probable that some of the observed associations were due to chance. Small sample sizes limited the power to detect an association with exposures of interest among less common histologic subtypes. A large portion of the nonparticipating patients were HIV-positive and therefore would not have an impact on these results, but patients over 55 years of age with high-grade NHL, although few in number, were less likely to have been interviewed (27). Immunoblastic

TABLE 5. Multivariable* age- and sex-adjusted odds ratios for non-Hodgkin lymphoma according to medical history, by Working Formulation† classification histologic subtype and two Revised European-American Lymphoma classification subtypes, among men and women who were negative for human immunodeficiency virus, San Francisco Bay Area, California, 1988–1995

Medical history factor	Working Formulation and ad hoc REAL‡ classification subtypes									
	Small lymphocytic (*n* = 152)		REAL follicular (FSC, FM, FL)‡ (*n* = 352)		Diffuse small cleaved-cell (*n* = 68)		Diffuse mixed small cleaved and large-cell (*n* = 75)		REAL diffuse large-cell (DL, IBL)‡ (*n* = 510)	
	OR‡	95% CI‡	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Receipt of vaccines										
Bacillus Calmette-Guérin	2.9	1.2, 7.0							1.8	0.93, 3.5
Hepatitis									0.70	0.50, 0.98
Diphtheria-pertussis-tetanus							0.44	0.26, 0.74		
Measles					0.52	0.26, 1.0				
≥5 vaccines§									0.65	0.52, 0.82
Use of medications										
Nonsteroidal antiinflammatory drugs	0.30	0.14, 0.66	0.67	0.44, 1.0						
Cimetidine plus¶	4.6	1.7, 13							2.4	1.1, 5.4
Noninsulin drugs for diabetes mellitus			0.29	0.10, 0.82			2.8	1.2, 6.9		
Beta-blockers			2.5	0.90, 7.0						
Calcium channel blockers									0.35	0.15, 0.82
Sulfonamides plus#									3.6	1.6, 8.4
Diseases/conditions										
Heart disease	1.6	1.0, 2.6	1.5	1.0, 2.1						
Hepatitis			0.36	0.17, 0.74						
Previous cancer									0.63	0.41, 0.94
Mononucleosis									0.55	0.33, 0.91
Childhood eczema									2.0	1.2, 3.2
Fever blisters									0.76	0.59, 0.96
Nonrheumatoid arthritis					0.39	0.15, 1.0				
Allergies										
Plants, etc.**	0.57	0.36, 0.92							0.72	0.55, 0.94
Animal dander									0.40	0.21, 0.73
Other factors										
≥3 bee or wasp stings	0.57	0.39, 0.84	0.79	0.62, 1.0						

* From stepwise parsimonious models fitted for specific non-Hodgkin lymphoma histologic subtypes.
† Developed by the Non-Hodgkin's Lymphoma Classification Project (36).
‡ REAL, Revised European-American Lymphoma; FSC, follicular small cleaved-cell; FM, follicular mixed small cleaved and diffuse-cell; FL, follicular large-cell; DL, diffuse large-cell; IBL, immunoblastic large-cell; OR, odds ratio; CI, confidence interval.
§ Diphtheria-pertussis-tetanus was counted as one vaccine.
¶ Cimetidine and another histamine-2 receptor antagonist.
# Sulfonamides and other antibacterial agents.
** Grass, trees, pollen, ragweed, hay fever, seasonal allergies, etc.

lymphomas were the most likely to have been underrepresented, and we combined these for all analyses to create the REAL large-cell category. Despite the loss of these cases, the proportion of high-grade Working Formulation cases by subtype in our population reflected that reported for other developed western populations (41).

The role of immunologic challenges in the development of immune-related disease as explained by the "hygiene hypothesis" (42) and the "Th1/Th2 paradigm" (43) may help to clarify the etiology of NHL, although neither theory is sufficient to completely describe immune function in our results. Both purport that a shift in the balance of T helper type 1 (Th1) cells to T helper type 2 (Th2) cells associated with environmental exposures may explain the changed incidence of some immune-related diseases. The hygiene hypothesis suggests that the decrease in early childhood infections has altered the balance from Th1 cells to Th2 cells, resulting in exaggerated immune reactions to antigens (43–46) that are characteristic of allergies and asthma.

Vaccines

There was a consistent pattern of decreased risk of NHL by subtype associated with vaccine history, except for BCG vaccine. Elevated risk of NHL associated with receipt of BCG vaccine has been reported previously (47) and is somewhat supported by results from studies evaluating cancer incidence after BCG vaccination (48, 49). Most participants

in our study who had received BCG vaccine were vaccinated during childhood while living outside of the United States. Unknown lifestyle factors related to living abroad may be associated with both increased risk of lymphoma and BCG vaccination. Our results for possible polio vaccine-related exposure to simian virus 40 and risk of NHL subtypes are consistent with negative data from other epidemiologic studies of cancer (50, 51) and are not consistent with recently published laboratory data showing the presence in NHL tumors of the simian virus 40 strain that contaminated the early polio vaccines (52, 53). Other vaccines have been associated with decreased risk of all NHL: injectable polio vaccine in women, cholera vaccine in men, and yellow fever vaccine in both women and men (15, 54). We found no epidemiologic data that pertained to vaccine history and risk of NHL by histologic subtype in a Medline search of articles published in English.

The vaccines were a mix of live attenuated virus, killed inactivated virus, toxoids, and gamma globulin. Age at first immunization was not available for many common childhood vaccines; therefore, possible effects associated with age at immunization and with changes in the vaccine could not be evaluated (e.g., measles vaccine contained killed virus between 1963 and 1967 and live virus starting in 1968). Most vaccines function to produce active immunity (Th1-dominant), with an antibody response similar to that generated by actual infection. The strength of the response is dependent on vaccine type, which explains why some vaccines require booster shots. Immune systems primed with vaccines to eradicate a variety of foreign invaders imply the proper functioning of B- and T-cell immune responses. This may partly explain the reduced risk of several subtypes of lymphoma and also may promote Th1 responses thought to be protective against cancer (55). However, a cohesive picture of the immunologic role vaccines may play in the development of some NHL subtypes is unknown.

Medications

Similar to our results, medications have been associated with reduced risk of other cancers, such as the reduced risk of colon cancer provided by NSAIDs (56–59), but little comparative epidemiologic information has been published about medications and risk of NHL by subtype. A case-control study conducted in Yorkshire, United Kingdom (437 cases and 724 controls), that compared risk factors for low- and high-grade NHL reported an increased risk of low-grade NHL associated with use of diabetes medications and an increased risk of high-grade NHL associated with use of steroids and antihistamines (18). We found no association by subtype with use of steroids and a nonsignificant reduced risk for antihistamine use. Nearly 91 percent of participants who reported antihistamine use and 41 percent of nonusers also reported a history of nonmedication allergies. When results were adjusted for allergy history, the reduced risks associated with antihistamine use were no longer apparent for REAL large-cell lymphoma and approached unity for small lymphocytic lymphoma. This fits with our original hypothesis that antihistamines would not be protective themselves but would be a measure of allergy severity and that persons with more symptoms would use antihistamines.

The nearly threefold risk of diffuse mixed-cell lymphoma among users of noninsulin diabetes medication was consistent with the threefold risk estimate associated with adult-onset diabetes. In contrast, use of noninsulin medications was associated with a 70 percent decreased risk of REAL follicular lymphoma, but diabetes was not independently associated with this NHL subtype.

Other medications of interest were likely to have been prescribed for conditions that can result in chronic inflammation. Among these other medications, cimetidine has been investigated as a possible carcinogen and has been determined by the International Agency for Research on Cancer to be "unclassifiable as to carcinogenicity to humans" (60). Cimetidine and other histamine-2 receptor antagonists have immunomodulatory effects (61, 62), with cimetidine having the most pronounced effects of all of these drugs (63). Use of cimetidine alone by participants with ulcers was not a risk factor for NHL, whereas use of cimetidine and another histamine-2 receptor antagonist was associated with 2- to 4.5-fold increased risks of two subtypes. Users of these medications may have had undiagnosed *H. pylori*-related ulcers that required an antibiotic regimen. Untreated symptomatic *H. pylori* infection has been associated with gastric cancer and with mucosa-associated lymphatic tissue lymphoma, a REAL subtype categorized within the Working Formulation small lymphocytic lymphomas (37, 38). Therefore, use of cimetidine and another histamine-2 receptor antagonist may have been a marker for chronic underlying *H. pylori* infection.

Use of sulfonamides and other antibacterial drugs was associated with a 3.5-fold increased risk of REAL large-cell lymphoma in the multivariable model. These drugs are typically used to treat bacterial infections such as urinary tract infections. There are no published data that link use of these drugs with risk of NHL. Because chronic bacterial infections previously have been associated with less than twofold increased risks of NHL (47, 64), the long-term use of these medications in our study may be a marker for chronic underlying infection. However, the risk of NHL associated with self-reported bacterial infections has sometimes conflicted with the corresponding risk estimate for antibacterial use. When these factors were adjusted for simultaneously in statistical models, each was an independent risk factor for NHL subtypes with no confounding observed.

Beta-blockers and calcium channel blockers are often prescribed for hypertension, a condition that can result from arterial plaque build-up, recently hypothesized to be associated with chronic infections and inflammation (65, 66). Beta-blockers influence immune regulation and cell processes associated with tumor growth (67, 68), whereas calcium channel blockers interfere with cell apoptosis (69). Both have been investigated in association with cancer risk, and most studies have reported little to no effect (69–71). Results for use of beta-blockers for conditions other than high blood pressure were consistent with results for heart disease, whereas findings for non-high-blood-pressure use of calcium channel blockers were different from those for heart disease. Statistical models that adjusted for the potentially confounding effects of these medications with each

other and with heart disease showed generally consistent associations with no confounding. The differential effects in our study may be related to different drug pathways, to inherent differences between persons prescribed beta-blockers and those prescribed calcium channel blockers, or to differences in underlying conditions. Additionally, low numbers may be a factor, although the patterns of association remained consistent across histologic subtypes, somewhat contradicting the instability usually associated with low numbers. Further research is needed to explain the possible role of these drugs in lymphomagenesis.

Consistent with results from our analyses of all NHL (15), decreased risks for Working Formulation low-grade NHL subtypes were associated with a history of NSAID use. NSAIDs disrupt the inflammatory process by blocking cyclooxygenase 1 and cyclooxygenase 2 synthesis that in turn inhibits synthesis of prostaglandins involved in the inflammatory process. Cyclooxygenase 2 promotes cell growth and differentiation and is induced in inflammation. Its inhibition by NSAIDs may induce apoptosis of cancer cells (72). NSAID use has been associated with a decreased risk of several cancers: colorectal (56–59, 73), pancreas (74), bladder (75), breast (76, 77), prostate (78), esophageal (79, 80), gastric (79), and ovarian (81). Although reason for use was not ascertained, it is likely that many arthritis patients are regular users of NSAIDs. Among study participants who first used NSAIDs at least 5 years before diagnosis or interview, 10 percent reported rheumatoid arthritis and 42 percent reported nonrheumatoid arthritis as compared with less than 2 percent and 11 percent of nonusers, respectively. When these factors were simultaneously adjusted for in statistical models, subtype estimates for NSAID use were unaffected. However, the elevated risk of small lymphocytic lymphoma associated with history of nonrheumatoid arthritis increased to 1.7.

Diseases and conditions

Risks of NHL subtypes associated with some diseases were inconsistent with results associated with medications prescribed to treat these conditions, as described above. In multivariable models, these diseases were associated more frequently with REAL large-cell lymphoma than with other subtypes and tended to confer a reduced risk. Heart disease and childhood eczema were the only conditions associated with increased risks of NHL subtypes, and heart disease was associated with risk of more than one subtype. Some heart disease is thought to have an infectious component that can result in chronic inflammation (65, 66). Infectious agents play a complex role in the development of immunologic cancers, and the number, type, and timing of bacterial and viral infections are important factors.

A growing body of work has accumulated on the association between allergic conditions and cancer risk. Childhood eczema is among the type 1 hypersensitivities typically associated with atopy, and its association with risk of lymphoma in our study is consistent with relations predicted by the "hygiene hypothesis." One earlier NHL study reported an elevated risk of high-grade lymphoma associated with eczema (18) but did not distinguish childhood eczema from adult eczema. Childhood eczema is susceptible to differential recall and bias. It is possible that only persons with severe and/or long-lasting eczema recalled the condition, and the observed association may be unique to this subgroup of patients with childhood eczema. Similarly, the association with hives as a result of unknown allergies may be related to recall bias or misclassification, since reports of hives or urticaria alone were not associated with NHL subtypes. Furthermore, hives may result from nonallergic conditions. Allergies have been associated with reduced risk of several other cancers (82–85), and allergic individuals may have more efficient immune systems, as required by B-cell activation for isotype switching to immunoglobulin E. Because allergies typically promote a Th2 (tumor-promoting) response, their etiologic role in cancer immunology is unclear. Our allergy findings are consistent with our earlier results for all NHL (15, 24) and differ from the findings of a smaller study (16). Several previous studies have investigated the association between allergies and risk of all NHL, but results have been inconsistent (as reviewed by Briggs et al. (16)).

The association with number of bee or wasp stings as opposed to allergy to these stings is consistent with our results for all NHL (15). These observations may be related to the few participants who reported this type of allergic reaction and the underlying effects of bee venom that have been associated with relief of certain immunologic conditions (86). Too few systemic responses were reported for separate analysis. A clinical trial is under way at Georgetown University Medical Center to investigate bee venom's impact on immune function.

Our results cannot be completely explained by the Th1/Th2 theories of immune function. Some observed associations may have been due to chance, with low numbers in some histologic groups, and the findings should be interpreted with caution. Given the general lack of information about risk factors for NHL by subtype, our results provide direction for further investigations of immune-system function, lymphomagenesis, and differences by NHL subtype. Advances in the understanding of cancer and the intricacies of the immune system will enable us to clarify how exposures that alter immune function contribute to the development of NHL. Large epidemiologic studies conducted by investigators from a range of scientific disciplines who can pool data with others are needed to determine etiologic clues for NHL by subtype.

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REFERENCES

1. Zheng T, Mayne ST, Boyle P, et al. Epidemiology of non-Hodgkin lymphoma in Connecticut. Cancer 1992;70:840–9.
2. Devesa SS, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res 1992; 52(suppl):5432s–40s.
3. Ries LA, Eisner MP, Kosary CL, et al. SEER cancer statistics review, 1973–1998. Bethesda, MD: National Cancer Institute, 2001.
4. Clarke CA, Glaser SL. Changing incidence of non-Hodgkin lymphomas in the United States. Cancer 2002;94:2015–23.
5. Hartge P, Devesa SS, Fraumeni JF Jr. Hodgkin's and non-Hodgkin's lymphomas. Cancer Surv 1994;19-20:423–53.
6. Mackay IR, Rose NR. Autoimmunity and lymphoma: tribulations of B cells. Nat Immunol 2001;2:793–5.
7. Shpilberg O, Wilson J, Whiteside TL, et al. Pre-transplant immunological profile and risk factor analysis of post-transplant lymphoproliferative disease development: the results of a nested matched case-control study. The University of Pittsburgh PTLD Study Group. Leuk Lymphoma 1999;36:109–21.
8. Cockfield SM. Identifying the patient at risk for post-transplant lymphoproliferative disorder. Transpl Infect Dis 2001;3:70–8.
9. Ziegler JL, Beckstead JA, Volberding PA, et al. Non-Hodgkin's lymphoma in 90 homosexual men: relation to generalized lymphadenopathy and the acquired immunodeficiency syndrome. N Engl J Med 1984;311:565–70.
10. Kassan SS, Thomas TL, Moutsopoulos HM, et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978;89: 888–92.
11. Filipovich AH, Zerbe D, Spector BD, et al. Lymphomas in persons with naturally occurring immunodeficiency disorders. In: Magrath IT, O'Conor GT, Ramot B, eds. Pathogenesis of leukemia and lymphomas: environmental influences. New York, NY: Raven Press, 1984:225–34.
12. Mueller NE, Mohar A, Evans A. Viruses other than HIV and non-Hodgkin's lymphoma. Cancer Res 1992;52(suppl):5479s–81s.
13. Manns A, Cleghorn FR, Falk RT, et al. Role of HTLV-I in development of non-Hodgkin lymphoma in Jamaica and Trinidad and Tobago. Lancet 1993;342:1447–50.
14. Tielsch JM, Linet MS, Szklo M. Acquired disorders affecting the immune system and non-Hodgkin's lymphoma. Prev Med 1987;16:96–106.
15. Holly EA, Lele C, Bracci PM, et al. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. Am J Epidemiol 1999; 150:375–89.
16. Briggs NC, Levine RS, Brann EA. Allergies and risk of non-Hodgkin's lymphoma by subtype. Cancer Epidemiol Biomarkers Prev 2002;11:401–7.
17. Vallisa D, Berte R, Rocca A, et al. Association between hepatitis C virus and non-Hodgkin's lymphoma, and effects of viral infection on histologic subtype and clinical course. Am J Med 1999;106:556–60.
18. Cartwright RA, McKinney PA, O'Brien C, et al. Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. Leuk Res 1988;12:81–8.
19. Parsonnet J. Gastric adenocarcinoma and *Helicobacter pylori* infection. West J Med 1994;161:60.
20. Vineis P, Crosignani P, Sacerdote C, et al. Hematopoietic cancer and peptic ulcer: a multicenter case-control study. Carcinogenesis 1999;20:1459–63.
21. Brandt L, Brandt J, Olsson H, et al. Blood transfusion as a risk factor for non-Hodgkin lymphoma. Br J Cancer 1996;73:1148–51.
22. Chow EJ, Holly EA. Blood transfusions as a risk factor for non-Hodgkin's lymphoma in the San Francisco Bay Area: a population-based study. Am J Epidemiol 2002;155:725–31.
23. Holly EA. Melanoma and pregnancy: a brief review. Recent Results Cancer Res 1986;102:118–26.
24. Holly EA, Lele C. Non-Hodgkin's lymphoma in HIV-positive and HIV-negative homosexual men in the San Francisco Bay Area: allergies, prior medication use and sex practices. J Acquir Immune Defic Syndr 1997;15:211–22.
25. Holly EA, Lele C, Bracci P. Non-Hodgkin's lymphoma in homosexual men in the San Francisco Bay Area: occupational, chemical and environmental exposures. J Acquir Immune Defic Syndr 1997;15:223–31.
26. Holly EA, Lele C, Bracci PM. Hair-color products and risk for non-Hodgkin's lymphoma: a population-based study in the San Francisco Bay Area. Am J Public Health 1998;88:1767–73.
27. Holly EA, Gautam M, Bracci PM. Comparison of interviewed and non-interviewed non-Hodgkin's lymphoma (NHL) patients in the San Francisco Bay Area. Ann Epidemiol 2002;12:419–25.
28. Kamel OW, Holly EA, van de Rijn M, et al. A population based, case control study of non-Hodgkin's lymphoma in patients with rheumatoid arthritis. J Rheumatol 1999;26:1676–80.
29. Tiirikainen MI, Mullaney BP, Holly EA, et al. DNA copy number alterations in HIV-positive and HIV-negative patients with diffuse large-cell lymphomas. J Acquir Immune Defic Syndr 2001;27:272–6.
30. Gaidano G, Dalla-Favera R. Molecular biology of lymphoid neoplasms. In: Mendelsohn J, Howley PM, Israel MA, et al, eds. The molecular basis of cancer. Philadelphia, PA: W B Saunders Company, 1995:251–79.
31. Macintyre E, Willerford D, Morris SW. Non-Hodgkin's lymphoma: molecular features of B cell lymphoma. Hematology (Am Soc Hematol Educ Program) 2000:180–204.
32. Alizadeh AA, Eisen MB, Davis RE, et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503–11.
33. Waksberg J. Sampling methods for random digit dialing. J Am Stat Assoc 1978;73:40–6.
34. Hartge P, Brinton LA, Rosenthal JF, et al. Random digit dialing in selecting a population-based control group. Am J Epidemiol 1984;120:825–33.
35. Lele C, Holly EA, Roseman DS, et al. Comparison of control subjects recruited by random digit dialing and area survey. Am J Epidemiol 1994;140:643–8.
36. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: summary and description of a working formulation for clinical usage. Cancer 1982;49: 2112–35.
37. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood 1994;84:1361–92.
38. Pittaluga S, Bijnens L, Teodorovic I, et al. Clinical analysis of 670 cases in two trials of the European Organization for the Research and Treatment of Cancer Lymphoma Cooperative Group subtyped according to the Revised European-American Classification of Lymphoid Neoplasms: a comparison with the Working Formulation. Blood 1996;87:4358–67.
39. Sweetenham JW, Smartt PF, Wilkins BS, et al. The clinical utility of the Revised European-American Lymphoma (R.E.A.L.) classification: preliminary results of a prospective study in patients with non-Hodgkin's lymphoma from a single centre. Ann Oncol 1999;10:1121–4.

40. Kelsey J, Whittemore A, Evans A, et al. Methods in observational epidemiology. New York, NY: Oxford University Press, 1996.
41. Jaffe E, Harris N, Stein H, et al. World Health Organization classification of tumours: pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon, France: International Agency for Research on Cancer, 2001.
42. Martinez FD. The coming-of-age of the hygiene hypothesis. Respir Res 2001;2:129–32.
43. Spellberg B, Edwards JJ Jr. Type 1/type 2 immunity in infectious diseases. Clin Infect Dis 2001;32:76–102.
44. Lappin MB, Campbell JD. The Th1-Th2 classification of cellular immune responses: concepts, current thinking and applications in haematological malignancy. Blood Rev 2000;14:228–39.
45. Constant SL, Bottomly K. Induction of Th1 and Th2 CD4+ T cell responses: the alternative approaches. Annu Rev Immunol 1997;15:297–322.
46. Wold AE. The hygiene hypothesis revised: is the rising frequency of allergy due to changes in the intestinal flora? Allergy 1998;53:20–5.
47. Tavani A, La Vecchia C, Franceschi S, et al. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. Eur J Cancer Prev 2000;9:59–64.
48. Snider DE, Comstock GW, Martinez I, et al. Efficacy of BCG vaccination in prevention of cancer: an update. J Natl Cancer Inst 1978;60:785–8.
49. Kendrick MA, Comstock GW. BCG vaccination and the subsequent development of cancer in humans. J Natl Cancer Inst 1981;66:431–7.
50. Strickler HD, Goedert JJ. Exposure to SV40-contaminated poliovirus vaccine and the risk of cancer—a review of the epidemiological evidence. Dev Biol Stand 1998;94:235–44.
51. Ferber D. Virology. Monkey virus link to cancer grows stronger. Science 2002;296:1012–15.
52. Vilchez RA, Madden CR, Kozinetz CA, et al. Association between simian virus 40 and non-Hodgkin lymphoma. Lancet 2002;359:817–23.
53. Shivapurkar N, Harada K, Reddy J, et al. Presence of simian virus 40 DNA sequences in human lymphomas. Lancet 2002; 359:851–2.
54. Bernstein L, Ross RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. Cancer Res 1992;52(suppl):5510s–15s.
55. Nishimura T, Nakui M, Sato M, et al. The critical role of Th1-dominant immunity in tumor immunology. Cancer Chemother Pharmacol 2000;46(suppl):S52–61.
56. Coogan PF, Rosenberg L, Louik C, et al. NSAIDs and risk of colorectal cancer according to presence or absence of family history of the disease. Cancer Causes Control 2000;11:249–55.
57. Collet JP, Sharpe C, Belzile E, et al. Colorectal cancer prevention by non-steroidal anti-inflammatory drugs: effects of dosage and timing. Br J Cancer 1999;81:62–8.
58. Garcia Rodriguez L, Huerta-Alvarez C. Reduced incidence of colorectal adenoma among long-term users of nonsteroidal antiinflammatory drugs: a pooled analysis of published studies and a new population-based study. Epidemiology 2000;11: 376–81.
59. Smalley W, Ray WA, Daugherty J, et al. Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study. Arch Intern Med 1999;159:161–6.
60. International Agency for Research on Cancer. Pharmaceutical drugs. (IARC monographs on the evaluation of carcinogenic risks to humans, vol 50). Lyon, France: International Agency for Research on Cancer, 1990:235–63.
61. Jutel M, Watanabe T, Klunker S, et al. Histamine regulates T-cell and antibody responses by differential expression of H_1 and H_2 receptors. Nature 2001;413:420–5.
62. Elenkov IJ, Webster E, Papanicolaou DA, et al. Histamine potently suppresses human IL-12 and stimulates IL-10 production via H_2 receptors. J Immunol 1998;161:2586–93.
63. Hahm KB, Kim WH, Lee SI, et al. Comparison of immunomodulative effects of the histamine-2 receptor antagonists cimetidine, ranitidine, and famotidine on peripheral blood mononuclear cells in gastric cancer patients. Scand J Gastroenterol 1995;30:265–71.
64. La Vecchia C, Negri E, Franceschi S. Medical history and the risk of non-Hodgkin's lymphomas. Cancer Epidemiol Biomarkers Prev 1992;1:533–6.
65. Kiechl S, Egger G, Mayr M, et al. Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. Circulation 2001;103:1064–70.
66. Siscovick DS, Schwartz SM, Corey L, et al. *Chlamydia pneumoniae*, herpes simplex virus type 1, and cytomegalovirus and incident myocardial infarction and coronary heart disease death in older adults: The Cardiovascular Health Study. Circulation 2000;102:2335–40.
67. Draoui A, Vandewalle B, Hornez L, et al. Beta-adrenergic receptors in human breast cancer: identification, characterization and correlation with progesterone and estradiol receptors. Anticancer Res 1991;11:677–80.
68. Elenkov IJ, Papanicolaou DA, Wilder RL, et al. Modulatory effects of glucocorticoids and catecholamines on human interleukin-12 and interleukin-10 production: clinical implications. Proc Assoc Am Physicians 1996;108:374–81.
69. Mason RP. Calcium channel blockers, apoptosis and cancer: is there a biologic relationship? J Am Coll Cardiol 1999;34:1857–66.
70. Meier CR, Derby LE, Jick SS, et al. Angiotensin-converting enzyme inhibitors, calcium channel blockers, and breast cancer. Arch Intern Med 2000;160:349–53.
71. Hole DJ, Hawthorne VM, Isles CG, et al. Incidence of and mortality from cancer in hypertensive patients. BMJ 1993;306: 609–11.
72. Shiff SJ, Koutsos MI, Qiao L, et al. Nonsteroidal antiinflammatory drugs inhibit the proliferation of colon adenocarcinoma cells: effects on cell cycle and apoptosis. Exp Cell Res 1996; 222:179–88.
73. Bigler J, Whitton J, Lampe JW, et al. *CYP2C9* and *UGT1A6* genotypes modulate the protective effect of aspirin on colon adenoma risk. Cancer Res 2001;61:3566–9.
74. Anderson KE, Johnson TW, Lazovich D, et al. Association between nonsteroidal anti-inflammatory drug use and the incidence of pancreatic cancer. J Natl Cancer Inst 2002;94:1168–71.
75. Castelao JE, Yuan JM, Gago-Dominguez M, et al. Non-steroidal anti-inflammatory drugs and bladder cancer prevention. Br J Cancer 2000;82:1364–9.
76. Sharpe CR, Collet JP, McNutt M, et al. Nested case-control study of the effects of non-steroidal anti-inflammatory drugs on breast cancer risk and stage. Br J Cancer 2000;83:112–20.
77. Harris RE, Kasbari S, Farrar WB. Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer. Oncol Rep 1999;6:71–3.
78. Norrish AE, Jackson RT, McRae CU. Non-steroidal anti-inflammatory drugs and prostate cancer progression. Int J Cancer 1998;77:511–15.
79. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 1998;7:97–102.

80. Funkhouser EM, Sharp GB. Aspirin and reduced risk of esophageal carcinoma. Cancer 1995;76:1116–19.
81. Cramer DW, Harlow BL, Titus-Ernstoff L, et al. Over-the-counter analgesics and risk of ovarian cancer. Lancet 1998;351:104–7.
82. Negri E, Bosetti C, La Vecchia C, et al. Allergy and other selected diseases and risk of colorectal cancer. Eur J Cancer 1999;35:1838–41.
83. Dai Q, Zheng W, Ji BT, et al. Prior immunity-related medical conditions and oesophageal cancer risk: a population-based case-control study in Shanghai. Eur J Cancer Prev 1997;6:152–7.
84. Wiemels JL, Wiencke JK, Sison JD, et al. History of allergies among adults with glioma and controls. Int J Cancer 2002;98:609–15.
85. Wen W, Shu XO, Linet MS, et al. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). Cancer Causes Control 2000;11:303–7.
86. Kwon YB, Lee HJ, Han HJ, et al. The water-soluble fraction of bee venom produces antinociceptive and anti-inflammatory effects on rheumatoid arthritis in rats. Life Sci 2002;71:191–204.