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Case-Control Study of Non-Hodgkin's Lymphoma among Women and Heterosexual Men in the San Francisco Bay Area, California

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A population-based case-control study was conducted between 1988 and 1995 in the San Francisco Bay Area of California to determine risk factors for non-Hodgkin's lymphoma. Participants completed in-person interviews, and blood was drawn to test for viruses and lymphocyte subsets. This report includes data for 1,281 cases and 2,095 controls. In multivariate analyses, the factors associated with a decreased risk for non-Hodgkin's lymphoma were allergy to plants, bee and wasp stings, five or more vaccinations, drugs to lower blood cholesterol, nonsteroidal anti-inflammatory drugs, total number of sexual partners, and lifetime marijuana use, whereas an increased risk was associated with cimetidine and other histamine H_2-receptor antagonists, splenectomy, gonorrhea, and body mass index. Unique to sex-specific models was an increased risk for endocrine gland disorders among women and for polio among men. Median CD3, CD4, CD8, CD20, and lymphocyte counts for non-Hodgkin's lymphoma patients were significantly lower than those for controls. These results implicate environmental factors that may influence the early stages of lymphomagenesis by stimulating the immune system. Antigen-driven B cells that accumulate to form lymphoma may be suppressed by immunologic stresses such as exposure to an increased number of sexual partners and to certain medications. A history of allergies provides evidence for a persistent capacity for B-cell differentiation and therefore a decreased accumulation of B cells. The decreased risk for non-Hodgkin's lymphoma with use of nonsteroidal anti-inflammatory drugs and cholesterol-lowering drugs is consistent with a macrophage inflammatory role in B-cell proliferation. *Am J Epidemiol* 1999;150:375–89.

allergy and immunology; case-control studies; hypersensitivity; immunization; immunosuppression; life style; lymphoma, non-Hodgkin's; risk factors

The annual percentage increase in non-Hodgkin's lymphoma of nearly 4 percent among men and 3 percent among women has exceeded the increases for all other cancers except melanoma of the skin, lung cancer among women (1, 2), and prostate cancer (1), which has been highly influenced by prostate-specific antigen testing. Despite this increased incidence, few risk factors for non-Hodgkin's lymphoma are known, and they do not explain the emerging epidemic (2, 3). Increased chronologic age, immunodeficiency, genetic susceptibility, antigenic stimulation, and chromosomal rearrangement are pathogenic factors that have been found to be associated with the process of lymphomagenesis (4). The individual and interactive effects of these factors and their role in the etiology of non-Hodgkin's lymphoma are complex and poorly defined. However, methodological advances in DNA and genetic testing, combined with evidence from clinical and epidemiologic studies, have helped to elucidate some of these processes.

Persons infected with the human immunodeficiency virus (HIV) are at increased risk for the development of high-grade non-Hodgkin's lymphoma (5). Because of the difference in incidence and related risk factors, the homosexual men who were included in our investigation were studied separately; results for these subjects have been published previously (6, 7). Our results regarding both HIV-positive and HIV-negative homosexual men showed a decreased risk for non-Hodgkin's lymphoma associated with an increased frequency of receptive anal intercourse and a history of allergies (6). HIV-positive homosexual men also had decreased risks associated with bee and wasp stings, a history of influenza vaccination, and a greater lifetime frequency of use of amphetamines (6).

This large, population-based case-control study was designed to investigate a priori hypotheses based on

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Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; HTLV, human T-lymphotrophic virus; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio.

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earlier research on the associations between non-Hodgkin's lymphoma and a history of use of immunosuppressant medications and immune-compromising medical conditions (8, 9), allergies (10), family medical history (11), exposures to viruses (12–16), lifestyle factors (17) including exposure to visitors from Africa (18), occupational history, and exposures to chemicals (19–22). The associations between non-Hodgkin's lymphoma and many of these exposures have been inconsistent across the published reports. Results presented here are for medical history, demographic, and lifestyle factors among women and heterosexual men who were diagnosed with non-Hodgkin's lymphoma and among their population-based heterosexual controls.

MATERIALS AND METHODS

Non-Hodgkin's lymphoma patients

Most non-Hodgkin's lymphoma patients in this study, which was conducted between 1988 and 1995, were identified within 1 month of diagnosis by using the Northern California Cancer Center's rapid case ascertainment system. As an additional check on our case-finding efforts, monthly Surveillance, Epidemiology, and End Results Program abstracts were used to identify persons with non-Hodgkin's lymphoma about 18–24 months after diagnosis. Eligible participants were between 21 and 74 years of age and resided in one of California's six San Francisco Bay Area counties at diagnosis. An independent pathology review was conducted by Dr. Ronald F. Dorfman at Stanford University to confirm initial diagnoses. After the pathology review, a total of 1,593 eligible non-Hodgkin's lymphoma patients completed in-person interviews. Of the 2,812 patients eligible for the study interview, 593 (21 percent) died before they could be contacted, 275 (10 percent) were too ill to be interviewed, 78 (3 percent) had medical contraindications to contact as reported by their physicians, 182 (6 percent) refused to participate, 74 (3 percent) could not be located, and 17 (<1 percent) were unavailable for other reasons. This report includes results from 580 women and 701 heterosexual men with non-Hodgkin's lymphoma. Included among these results are data on 17 HIV-positive patients, 2 women and 15 heterosexual men. Detailed procedures for all methods related to this study and the results for the remaining 312 homosexual men with non-Hodgkin's lymphoma were published in the first reports on HIV-related lymphomas (6, 7).

Controls

Controls were identified by using random digit dialing (23, 24) and were frequency-matched to patients by sex, county of residence, and age within 5 years. Details of the random digit dialing procedure used to identify controls have been reported previously (6). A total of 2,515 (78 percent) eligible controls completed interviews; of these, 838 women and 1,257 heterosexual men formed the control group for the present report. The remaining 420 controls were homosexual men included in the first reports on HIV-related lymphomas (6, 7). Among the controls, no women and one heterosexual man were HIV-positive.

Interviews

Structured, face-to-face interviews were conducted by trained interviewers in study subjects' homes or at places convenient to the subjects. Interview topics covered family and personal medical history and included details about common allergies, medical procedures and conditions such as autoimmune diseases, use of therapeutic drugs for at least 4 consecutive weeks, history of immunizations and viral infections, sexual history, use of tobacco and illicit drugs and consumption of alcohol, demographic characteristics, and family income. Detailed questions also were asked about exposures to chemicals during work, school, or leisure activities; job history; and travel to foreign countries. Most questions pertained to exposures or activities that excluded the year prior to the interview. No proxy interviews were conducted.

Laboratory specimens

Bloods were drawn from consenting participants who had no history of chemotherapy within the past 3 months. The specimens were analyzed for HIV and for human T-lymphotrophic virus (HTLV)-I and -II. Analyses for CD3, CD4, CD8, CD20, lymphocyte, and white blood cell counts were performed on blood drawn from participants who had not received chemotherapy. HIV and HTLV-I serologic testing was conducted by using enzyme-linked immunosorbent assay and Western blot assay (Diagnostic Biotech, Singapore). HTLV-II serology was performed on HTLV-I indeterminate specimens.

Statistical analysis

Unconditional logistic regression was used to obtain odds ratios as estimates of the relative risks for all factors. Odds ratios were first adjusted for age alone and later for potential confounders in multivariate models. Also computed were 95 percent confidence intervals for the odds ratios and associated two-tailed p values. In this report, effects are referred to as borderline when the p value is between 0.05 and 0.10. All possible associations, as well as interactions between predictors, were assessed.

All analyses were first stratified by sex. This report presents age-adjusted results separately when sex-specific odds ratios varied by more than 10 percent from the combined results and together when individual odds ratios were similar but small numbers of exposed participants precluded presenting meaningful results by sex. Multivariate models that considered the biology of the disease were fit separately by sex and for women and men combined. The small proportion (<1 percent) of HIV-positive heterosexual patients included in the analyses presented here had no effect on the risk estimates.

Age was categorized into nine groups for univariate analyses and as <55 or ≥55 years for the multivariate models. Other noncategorical covariates were considered binary, tertiles, or quartiles by using all controls, unless a paucity of measurements or the meaning of categories forced a slightly different classification. Medical conditions that occurred more than 5 years prior to the date of the interview were used in the analyses to avoid spurious associations with diseases diagnosed as a result of the onset of non-Hodgkin's lymphoma. Weight and height were considered together as body mass index (weight in kg/height in m^2) and were grouped for analyses as <20 (lean), 20–<25 (normal range), 25–<30 (class 1 overweight), and ≥30 (class 2 and class 3 overweight) (25).

Alcohol consumption data were collected as the number of drinks consumed per week of beer, wine, or liquor (one 12 oz can was defined as one drink of beer, one 4 oz glass as one drink of wine, and 1 oz of liquor as one drink of liquor; 1 oz = 30 ml) during the specific age intervals of 15–19, 20–29, 30–39, 40–49, 50–59, and ≥60 years. Total consumption for each person was calculated separately for beer, wine, and liquor by multiplying the number of drinks consumed by the number of years in each age interval and adding across intervals.

Participants who reported illicit use of a drug were asked to provide their age when the drug was first and last used and to specify their lifetime frequency of use as one of 12 categories. Data on the lifetime number of sexual partners also were collected as a categorical variable. Participants were asked to select one of 22 categories that best described their total number of sexual partners up to 1 year prior to the interview.

Many results from the age-adjusted analyses are presented in the text and tables of this report if they were found in previous studies or were of a priori interest. Age-adjusted results that were dissimilar in men and women or were based on small numbers are presented in the text only. However, most age-adjusted results are shown only in the tables. Factors found to be associated with non-Hodgkin's lymphoma when the multivariate analyses were conducted are discussed in the Multivariate Analysis portion and are omitted from the Age-adjusted Analyses portion of the Results section.

RESULTS

Age-adjusted analyses

Demographics and foreign travel. The distributions of demographic factors for non-Hodgkin's lymphoma cases and controls, by sex, are presented in table 1. The median ages of women with non-Hodgkin's lymphoma

TABLE 1. Demographic characteristics of women and heterosexual men with non-Hodgkin's lymphoma (NHL) and of controls, San Francisco Bay Area, California, 1988–1995*

Demographic characteristic	Women				Men			
	NHL patients (*n* = 580)		Controls (*n* = 838)		NHL patients (*n* = 701)		Controls (*n*= 1,257)	
	No.	%	No.	%	No.	%	No.	%
Education (highest grade completed)								
<12	76	13	72	9	81	12	78	6
12	207	36	265	32	173	25	244	19
13–15	130	22	233	28	157	22	295	24
16	84	14	154	18	148	21	289	23
≥17	83	14	114	14	141	20	350	28
Annual family income ($)								
<30,000	230	40	324	39	171	24	284	23
30,000–49,999	163	28	248	30	191	27	349	28
≥50,000	168	29	237	28	325	46	600	48
Race								
White, non-Hispanic	451	78	680	81	539	77	998	79
White, Hispanic	51	9	59	7	56	8	94	8
Black	30	5	44	5	38	5	78	6
Asian	40	7	45	5	55	8	68	5
Other	8	1	10	1	13	2	19	2

* The number of subjects may vary because of missing values.

TABLE 2. Odds ratios (OR) and 95% confidence intervals (CI) for non-Hodgkin's lymphoma (NHL) associated with personal characteristics and substance use among women and heterosexual men, San Francisco Bay Area, California, 1988–1995*

Personal characteristic or substance use	Women						Men					
	NHL patients (*n* = 580)		Controls (*n* = 838)		OR†	95% CI†	NHL patients (*n* = 701)		Controls (*n* = 1,257)		OR†	95% CI†
	No.	%	No.	%			No.	%	No.	%		
Body mass index (score)‡												
Lean (<20)	151	26	301	36	1.0		10	1	32	3	1.0	
Normal range (20–<25)	365	63	480	57	1.5	1.2, 1.9	291	42	611	49	1.5	0.74, 3.2
Class 1 overweight (25–<30)	42	7	45	5	1.9	1.2, 3.0	324	46	524	42	1.9	0.92, 3.9
Class 2 and 3 overweight (≥30)	17	3	11	1	3.1	1.4, 6.8	75	11	89	7	2.6	1.2, 5.7
p for trend					0.0001						0.0002	
No. of siblings§												
0	43	7	76	9	1.0		54	8	99	8	1.0	
1	114	20	194	23	1.1	0.67, 1.6	154	22	298	24	1.0	0.71, 1.5
2	109	19	164	20	1.2	0.75, 1.8	140	20	270	22	1.1	0.73, 1.6
3–4	151	26	213	25	1.3	0.82, 1.9	171	24	327	26	1.1	0.74, 1.6
≥5	159	27	185	22	1.5	0.98, 2.3	175	25	246	20	1.4	0.97, 2.1
p for trend					0.01						0.03	
Total no. of sexual partners												
≤1	284	49	303	36	1.0		147	21	206	16	1.0	
2–4	144	25	248	30	0.61	0.47, 0.79	160	23	267	21	0.88	0.66, 1.2
5–14	100	17	195	23	0.53	0.39, 0.71	207	30	370	29	0.88	0.67, 1.2
≥15	42	7	79	9	0.53	0.35, 0.82	167	24	379	30	0.68	0.51, 0.90
p for trend					<0.0001						0.01	
Smoking status												
Never smoked	283	49	408	49	1.0		237	34	487	39	1.0	
Ex-smoker	172	30	265	32	0.93	0.73, 1.2	324	46	507	40	1.1	0.91, 1.4
Current smoker	125	22	165	20	1.1	0.83, 1.4	139	20	263	21	1.1	0.81, 1.4
Lifetime consumption of beer, wine, and liquor¶												
None	220	38	255	30	1.0		138	20	205	16	1.0	
Low	116	20	189	23	0.71	0.53, 0.96	190	27	346	28	0.84	0.63, 1.1
Medium	124	21	194	23	0.74	0.56, 0.99	190	27	360	28	0.80	0.60, 1.1
High	120	21	200	24	0.70	0.52, 0.94	182	26	346	27	0.82	0.62, 1.1
Substance and no. of times used												
Marijuana												
Never	460	79	591	71	1.0		500	71	692	55	1.0	
<40	77	13	165	20	0.56	0.40, 0.77	109	16	264	21	0.64	0.49, 0.84
40–999	30	5	59	7	0.58	0.35, 0.97	62	9	198	16	0.52	0.37, 0.73
≥1,000	13	2	21	2	0.71	0.34, 1.5	29	4	100	8	0.49	0.31, 0.78

p for trend												0.0001
Cocaine/crack												
Never	531	92	743	89	1.0		609	87	994	79	1.0	
<20	29	5	66	8	0.63	0.39, 1.0	55	8	146	12	0.83	0.59, 1.2
≥20	20	3	27	3	1.0	0.56, 1.9	36	5	113	9	0.72	0.48, 1.1
p for trend												0.08
Speed, methamphetamine, or amphetamines												
Never	551	95	769	92	1.0		641	91	1,068	85	1.0	
<20	13	2	34	4	0.55	0.28, 1.1	27	4	102	8	0.58	0.37, 0.92
≥20	16	3	33	4	0.67	0.36, 1.3	33	5	84	7	0.86	0.56, 1.3
LSD (acid)												
Never	555	96	776	93	1.0		646	92	1,072	86	1.0	
<5	11	2	35	4	0.45	0.22, 0.92	28	4	69	6	0.87	0.54, 1.4
.≥5	14	2	25	3	0.78	0.40, 1.5	27	4	113	9	0.54	0.34, 0.84
p for trend												0.008
Amyl or butyl nitrite (poppers)												
No	566	98	818	98	1.0		685	98	1,189	95	1.0	
Yes	14	2	16	2	1.3	0.64, 2.8	16	2	65	5	0.58	0.33, 1.0

* The number of subjects may vary because of missing values.
† Adjusted for age.
‡ Computed as (weight in kg)/(height in m^2) on the basis of women's weight at age 25 years and men's usual adult weight.
§ Half-brothers and half-sisters were included.
¶ One drink was defined as 12 oz of beer, 4 oz of wine, or 1 oz of liquor; 1 oz = 30 ml. Cutpoints for lifetime average number of drinks/week were based on tertiles of the distribution among controls—women: low, ≤2.2; medium, >2.2–<5.8; high, ≥5.8; men: low, ≤5.5; medium, >5.5–<13.6; high ≥13.6.

and of their controls were 61.5 and 61 years, respectively. The respective median ages of heterosexual men were 58 and 53 years. Controls were slightly more educated than cases. These slight variations were not apparent when odds ratios were computed. Distributions also were similar between non-Hodgkin's lymphoma cases and controls by family income, race, and religion as a child (data for religion not shown).

Age-adjusted analyses showed a modest trend with an increased risk for non-Hodgkin's lymphoma associated with having an increasing number of siblings (table 2). Among women, being divorced (odds ratio (OR) = 0.51, 95 percent confidence interval (CI): 0.38, 0.68) or never having married (OR = 0.67, 95 percent CI: 0.46, 0.99) was associated with a decreased risk for non-Hodgkin's lymphoma compared with women who were married at the time of the interview (data not shown). Risk for non-Hodgkin's lymphoma was not associated with foreign travel or with contact with persons returning from Africa (data not shown).

Tobacco and illicit drug use and alcohol consumption. Ever having smoked cigarettes was not associated with risk for non-Hodgkin's lymphoma (table 2). Compared with participants who had no history of having regularly consumed at least one drink per month, consumers of alcohol had a slightly reduced risk for non-Hodgkin's lymphoma, particularly women (table 2). Individual results for beer, wine, and liquor showed somewhat similar effects (data not shown).

For men who used some illicit drugs, there was a trend toward a reduced risk for non-Hodgkin's lymphoma with increased frequency of substance use, whereas results were less consistent for women (table 2). Among men, a reduced risk also was associated with ever use of magic mushrooms or psilocybin (OR = 0.47, 95 percent CI: 0.24, 0.95) compared with never use of these substances. Intravenous drug use among HIV-negative subjects was analyzed by pooling over sex because of the small number of women who reported ever having injected drugs. Risk for non-Hodgkin's lymphoma was not associated with intravenous street-drug use regardless of whether needles were shared (ever shared needles, OR = 1.3, 95 percent CI: 0.58, 2.8; never shared needles, OR = 0.94, 95 percent CI: 0.29, 3.2). However, among HIV-negative subjects, analyses by specific drugs showed that ever having injected speed, methamphetamine, or other amphetamines was associated with a 5.7-fold increased risk for non-Hodgkin's lymphoma for women and men combined (95 percent CI: 1.8, 18; 10 non-Hodgkin's lymphoma patients exposed, 4 controls exposed).

Allergies. Among both the non-Hodgkin's lymphoma cases and the controls, a greater proportion of women than men reported having had allergies (table 3). Women and men who received regular injections to treat allergies and asthma also showed decreased risks for non-Hodgkin's lymphoma. Among women, significantly decreased risks were associated with allergies to medications, food, and dust, chalk, or mold and with a history of hives, whereas allergies to animals were associated with a decreased risk for non-Hodgkin's lymphoma among men.

Vaccinations and medications. Among women and men, a reduced risk for non-Hodgkin's lymphoma was associated with adult vaccination against several diseases and with an increase in the lifetime number of different types of vaccinations (table 3). Men had a reduced risk associated with childhood vaccination against diphtheria-pertussis-tetanus (OR = 0.83, 95 percent CI: 0.66, 1.0), measles (OR = 0.83, 95 percent CI: 0.67, 1.0), rubella (OR = 0.70, 95 percent CI: 0.54, 0.90), hepatitis (OR = 0.70, 95 percent CI: 0.51, 0.94), and polio, whereas there were no significant associations with childhood vaccinations among women (data not shown). Men who had non-Hodgkin's lymphoma were less likely to have been vaccinated against polio before age 10 years, but there was no association among women (table 3).

Subjects also were asked about their use of therapeutic medications for at least 4 consecutive weeks prior to 1 year before the interview (controls) or prior to 1 year before diagnosis (cases) (table 3). A reduced risk for non-Hodgkin's lymphoma was associated with use of diazepam among men (OR = 0.54, 95 percent CI: 0.33, 0.90). Among women and men, no risk for non-Hodgkin's lymphoma was associated with use of antibiotics, acetaminophen, medications for hypertension, steroids, or barbiturates; phenytoin sodium, allopurinol, insulin, or other drugs to control diabetes; or drugs to control weight.

Other health conditions and medical procedures. Among women, a reduced risk for non-Hodgkin's lymphoma was associated with a history of rubella (OR = 0.76, 95 percent CI: 0.60, 0.96), whooping cough (OR = 0.76, 95 percent CI: 0.60, 0.98), cold sores or fever blisters (OR = 0.78, 95 percent CI: 0.62, 0.98), canker sores (OR = 0.69, 95 percent CI: 0.55, 0.86), and tooth abscess (OR = 0.74, 95 percent CI: 0.58, 0.94). There was no further evidence of risk associated with a history of most other childhood and adult infectious and chronic disorders, including mononucleosis, sexually transmitted diseases other than gonorrhea, nonrheumatoid arthritis, autoimmune diseases, diabetes, heart disease, and diseases of other major organs (data not shown). A history of medical procedures such as diagnostic radiographic examinations, blood transfusions, appendectomy, tonsillectomy, or organ transplant (two non-Hodgkin's lymphoma patients reported kidney

transplants) also was not associated with risk for non-Hodgkin's lymphoma (data not shown).

Family history of hematopoietic cancer. A reported history of lymphoma, leukemia, or Hodgkin's disease in a parent, child, or sibling was associated with an elevated risk for non-Hodgkin's lymphoma among women (OR = 1.7, 95 percent CI: 1.1, 2.7), with a borderline result among men (OR = 1.5, 95 percent CI: 0.99, 2.3). In particular, a history of lymphoma in the immediate family was associated with an increased risk for non-Hodgkin's lymphoma (men, OR = 2.1, 95 percent CI: 1.0, 4.3; women, OR = 3.0, 95 percent CI: 1.4, 6.1). Also of interest were a husband and wife diagnosed with non-Hodgkin's lymphoma. Both were in their early fifties when diagnosed within 18 months of each other. They reported similar risks related to a history of exposures to chemicals and extended stays in rural Mexico.

Multivariate analysis

All models were adjusted for age and education; the combined model also was adjusted for sex (table 4). Each of the three models showed an independent risk for non-Hodgkin's lymphoma associated with allergy to grass, hay, trees, leaves, other plants, and pollen; three or more bee and wasp stings; five or more different types of vaccinations; use of nonsteroidal anti-inflammatory drugs (NSAIDs) (aspirin, enteric-coated aspirin, ibuprofen, naproxen, naproxen sodium, diflunisal, sulindac, indomethacin, salsalate, piroxicam, tolmetin sodium, diclofenac sodium, phenylbutazone, and ketoprofen); use of cholesterol-lowering drugs; use of cimetidine and other histamine H_2-receptor antagonists (ranitidine, famotidine, and nizatidine) to treat ulcers; body mass index score; and lifetime number of sexual partners. Most of these exposures were related to decreased risks for non-Hodgkin's lymphoma, with the exceptions of an increased risk related to an increased body mass index score and to the use of cimetidine and other histamine H_2-receptor antagonists.

In addition, in the individual models, women who reported non-thyroid-related endocrine gland disorders (pituitary, estrogen or other female hormone, adrenal, parathyroid, and hyperinsulinemia) had a 3.3-fold increased risk for non-Hodgkin's lymphoma, whereas men who had been diagnosed with polio had a 2.6-fold increased risk. The men's model and the combined model showed similar elevated risks for non-Hodgkin's lymphoma related to a history of gonorrhea and similar decreased risks associated with an increased lifetime frequency of marijuana use. An increased risk for non-Hodgkin's lymphoma associated with a history of splenectomy was significant only in the combined model, although sex-specific, age-adjusted risks were of similar magnitude.

Laboratory results

A total of 62 percent of eligible non-Hodgkin's lymphoma patients and 62 percent of controls signed separate consent forms to have their blood drawn. Values for each blood parameter were similar for women and men, and data were combined for analyses. The median CD3, CD4, CD8, CD20, and lymphocyte counts for non-Hodgkin's lymphoma patients were significantly lower than those for controls (table 5). One control and no non-Hodgkin's lymphoma patients were seropositive for HTLV-I, and no participants were seropositive for HTLV-II.

DISCUSSION

Epidemiologic significance

Risk factors for non-Hodgkin's lymphoma from the final multivariate models can be categorized into three broad groups of exposures related to the function and integrity of the immune system: use of medications, lifestyle factors, and medical history, including allergies and immunizations. After control for potential confounders, history of plant allergies, number of bee and wasp stings, number of different types of vaccinations, use of NSAIDs, use of cholesterol-lowering drugs, and lifetime number of sexual partners were independently associated with a decreased risk for non-Hodgkin's lymphoma among women and men. Increasing body mass index score, history of splenectomy, and use of cimetidine and other histamine H_2-receptor antagonists to treat ulcers were associated with an increased risk for non-Hodgkin's lymphoma. In addition, increased risks were found among women with non-thyroid-related endocrine gland disorders and among men who had a history of polio and gonorrhea. Risk for non-Hodgkin's lymphoma decreased with increased frequency of marijuana use among men but not among women.

A priori hypotheses about risk factors that affect immune system function, such as common allergies, bee and wasp stings, and immunizations, were based on etiologic clues from previous studies (5, 8–10, 12–17, 26) and were confirmed in the age-adjusted and multivariate analyses, both in the earlier analyses of homosexual men (6) and in the present analyses of women and heterosexual men. Studies of other cancers have reported reduced risks associated with allergy-related conditions (27–32), whereas for non-Hodgkin's lymphoma, results from earlier investigations have varied (6, 11, 33–35). Our results were consistent with earlier work, which found that women reported more allergies than men and that a decreased risk for cancer was associated with a history of allergy-related manifestations (30, 32). A reduced risk for non-Hodgkin's lymphoma

TABLE 3. Odds ratios (OR) and 95% confidence intervals (CI) for non-Hodgkin's lymphoma (NHL) associated with medical history among women and heterosexual men, San Francisco Bay Area, California, 1988–1995*

Medical history	Women						Men					
	NHL patients (n = 580)		Controls (n = 838)		OR†	95% CI†	NHL patients (n= 701)		Controls (n = 1,257)		OR†	95% CI†
	No.	%	No.	%			No.	%	No.	%		
Ever had allergic reaction to any medications												
No	403	70	530	63	1.0		554	79	1,012	81	1.0	
Yes	176	30	307	37	0.75	0.60, 0.94	147	21	243	19	1.0	0.81, 1.3
Ever had other nonmedication allergies												
No	308	53	383	46	1.0		431	62	696	55	1.0	
Yes	271	47	452	54	0.75	0.61, 0.93	268	38	557	44	0.83	0.68, 1.0
Food allergies												
No	484	83	669	80	1.0		621	89	1,108	88	1.0	
Yes	96	17	169	20	0.79	0.60, 1.0	80	11	149	12	0.96	0.71, 1.3
Allergy to grass, hay, trees, leaves, other plants, pollen												
No	515	89	679	81	1.0		631	90	1,046	83	1.0	
Yes	65	11	159	19	0.54	0.40, 0.74	70	10	211	17	0.58	0.44, 0.78
Allergy to dust, chalk, mold												
No	537	93	747	89	1.0		660	94	1,166	93	1.0	
Yes	43	7	91	11	0.66	0.45, 0.97	41	6	91	7	0.87	0.59, 1.3
Allergy to animals												
No	548	94	774	92	1.0		682	97	1,181	94	1.0	
Yes	32	6	64	8	0.72	0.46, 1.1	19	3	76	6	0.49	0.29, 0.82
Hives‡												
No	467	81	609	73	1.0		582	83	1,070	85	1.0	
Yes	110	19	221	26	0.65	0.50, 0.84	105	15	161	13	1.2	0.88, 1.5
Asthma‡												
No	540	93	767	92	1.0		642	92	1,139	91	1.0	
Yes	39	7	68	8	0.81	0.54, 1.2	50	7	104	8	0.87	0.61, 1.2
Had regular inoculations for allergies or asthma												
No	558	96	784	94	1.0		676	96	1,172	93	1.0	
Yes	22	4	54	6	0.57	0.34, 0.95	25	4	85	7	0.54	0.34, 0.85

Ever stung by a bee or wasp												
No	263	45	317	38	1.0		246	35	371	30	1.0	
Yes	315	54	517	62	0.74	0.60, 0.92	453	65	884	70	0.80	0.66, 0.98
No. of bee and wasp stings												
0	263	45	317	38	1.0		246	35	371	30	1.0	
1–2	168	29	236	28	0.86	0.67, 1.1	152	22	222	18	1.1	0.84, 1.4
3–6	99	17	187	22	0.64	0.48, 0.86	155	22	332	26	0.74	0.58, 0.96
≥7	45	8	87	10	0.63	0.43, 0.94	138	20	316	25	0.67	0.52, 0.87
p for trend					0.001						0.001	
Ever vaccinated against												
Smallpox												
No	131	23	153	18	1.0		148	21	210	17	1.0	
Yes	403	69	620	74	0.76	0.58, 0.99	493	70	941	75	0.77	0.60, 0.98
Cholera												
No	453	78	628	75	1.0		420	60	695	55	1.0	
Yes	70	12	143	17	0.68	0.50, 0.94	181	26	410	33	0.69	0.56, 0.86
Yellow fever												
No	494	85	682	81	1.0		455	65	767	61	1.0	
Yes	42	7	100	12	0.59	0.40, 0.86	152	22	347	28	0.70	0.56, 0.88
Influenza												
No	319	55	416	50	1.0		329	47	600	48	1.0	
Yes	253	44	400	48	0.80	0.64, 1.0	344	49	605	48	0.92	0.76, 1.1
Age at vaccination against polio												
Never	139	24	187	22	1.0		166	24	214	17	1.0	
≥10 years	322	56	480	57	0.91	0.70, 1.2	384	55	640	51	0.79	0.62, 1.0
≤9 years	63	11	106	13	0.91	0.56, 1.5	90	13	298	24	0.51	0.34, 0.76
p for trend											0.001	
Total no. of vaccinations§												
≤3	181	31	209	25	1.0		174	25	226	18	1.0	
4–5	204	35	297	35	0.80	0.61, 1.0	214	30	354	28	0.81	0.62, 1.1
≥6	195	34	332	40	0.69	0.52, 0.90	313	45	677	54	0.65	0.51, 0.83
p for trend					0.01						0.0004	

Table continues

TABLE 3. Continued

Medical history	Women						Men					
	NHL patients (*n* = 580)		Controls (*n* = 838)		OR†	95% CI†	NHL patients (*n* = 701)		Controls (*n* = 1,257)		OR†	95% CI†
	No.	%	No.	%			No.	%	No.	%		
Ever used the following medications for at least 4 consecutive weeks												
Cimetidine and other ulcer medications												
No	490	85	712	85	1.0		580	83	1,093	87	1.0	
Cimetidine and another histamine H_2-receptor antagonist	12	2	6	1	2.9	1.1, 7.8	10	1	9	1	1.8	0.74, 4.6
Nonsteroidal anti-inflammatory drugs												
No	526	91	724	86	1.0		639	91	1,131	90	1.0	
Yes	54	9	114	14	0.63	0.45, 0.89	62	9	126	10	0.74	0.53, 1.0
Drugs to lower blood cholesterol												
No	561	97	794	95	1.0		682	97	1,204	96	1.0	
Yes	19	3	43	5	0.60	0.35, 1.0	19	3	53	4	0.55	0.32, 0.94
Antibiotics												
No	560	97	794	95	1.0		673	96	1,201	96	1.0	
Yes	20	3	44	5	0.65	0.38, 1.1	28	4	56	4	1.0	0.64, 1.6
Ever had the following diseases or disorders												
Polio‡												
No	573	99	825	98	1.0		686	98	1,246	99	1.0	
Yes	7	1	13	2	0.75	0.30, 1.9	14	2	10	1	2.5	1.1, 5.7
Endocrine gland disorder‡												
No	570	98	831	99	1.0		696	99	1,249	99	1.0	
Yes	10	2	5	1	3.0	1.0, 8.7	5	1	7	1	1.3	0.41, 4.1
Gonorrhea												
No	565	97	814	97	1.0		644	92	1,170	93	1.0	
Yes	15	3	24	3	0.93	0.48, 1.8	55	8	71	6	1.5	1.0, 2.1
Men and women combined												
Splenectomy‡												
No	1,270	99							2,088	99.8	1.0	
Yes	8	1							4	0.2	3.6	1.1, 12

* The number of subjects may vary among factors because of missing values.
† Adjusted for age.
‡ Conditions that occurred more than 5 years before the diagnosis or interview date.
§ Includes tetanus vaccine, diphtheria-pertussis-tetanus vaccine, and tetanus shots after injury.

TABLE 4. Three separate multivariate models for non-Hodgkin's lymphoma in women and heterosexual men, San Francisco Bay Area, California, 1988–1995

Factors in model	Women*		Men*		Women and men combined†	
	OR	95% CI	OR	95% CI	OR	95% CI
Plant allergies						
No	1.0		1.0		1.0	
Yes	0.59	0.43, 0.81	0.60	0.45, 0.82	0.60	0.48, 0.75
No. of bee and wasp stings						
<3	1.0		1.0		1.0	
≥3	0.74	0.58, 0.95	0.72	0.59, 0.87	0.74	0.64, 0.86
No. of different vaccinations						
<5	1.0		1.0		1.0	
≥5	0.80	0.64, 1.0	0.76	0.62, 0.94	0.79	0.68, 0.92
Nonsteroidal anti-inflammatory drugs‡						
No	1.0		1.0		1.0	
Yes	0.70	0.49, 1.0	0.73	0.52, 1.0	0.72	0.56, 0.91
Cholesterol-lowering drugs‡						
No	1.0		1.0		1.0	
Yes	0.60	0.34, 1.1	0.57	0.33, 1.0	0.57	0.39, 0.85
Ulcer medications‡						
No	1.0		1.0		1.0	
Cimetidine and another histamine H_2-receptor antagonist	2.9	1.0, 8.0	1.8	0.69, 4.5	2.3	1.2, 4.6
Body mass index (score)§						
<20	1.0		1.0		1.0	
20–<25	1.5	1.2, 2.0	1.8	0.84, 3.7	1.6	1.2, 2.0
25–<30	1.9	1.2, 3.0	2.2	1.0, 4.6	2.0	1.5, 2.6
≥30	2.6	1.1, 5.8	2.8	1.3, 6.3	2.5	1.7, 3.7
Lifetime no. of sexual partners¶						
≤1	1.0		1.0		1.0	
2–4, 2–14	0.62	0.47, 0.81	0.95	0.73, 1.2	0.81	0.68, 0.98
≥5, ≥15	0.57	0.43, 0.76	0.68	0.50, 0.91	0.68	0.56, 0.84
Endocrine gland disorder ≥5 years ago						
No	1.0					
Yes	3.3	1.1, 10				
Gonorrhea#						
No			1.0		1.0	
Yes			1.8	1.2, 2.7	1.7	1.2, 2.3
Lifetime marijuana use						
Never			1.0		1.0	
<40 times			0.68	0.52, 0.91	0.68	0.55, 0.84
≥40 times			0.55	0.40, 0.76	0.57	0.44, 0.74
Polio ≥5 years ago						
No			1.0			
Yes			2.6	1.1, 6.0		
Splenectomy ≥5 years ago						
No					1.0	
Yes					5.0	1.4, 18

* Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age and education.
† OR and 95% CI adjusted for age, education, and sex.
‡ For 4 or more consecutive weeks.
§ Computed as (weight in kg)/(height in m^2) on the basis of women's weight at age 25 years and men's usual adult weight.
¶ Women, 2–4 and men, 2–14; women, ≥5 and men, ≥15.
# The risk associated with gonorrhea was found only in men.

TABLE 5. Blood parameters for women and heterosexual men with non-Hodgkin's lymphoma (NHL) and for controls, San Francisco Bay Area, California, 1988–1995*

Blood parameters (count in mm³)	Women and men combined						
	NHL patients (n = 237)			Controls (n = 1,251)			Wilcoxon p value†
	Quartile 1	Median	Quartile 3	Quartile 1	Median	Quartile 3	
White blood cells	4,500	6,000	7,800	4,900	6,100	7,500	0.95
Lymphocytes	850	1,305	2,060	1,187	1,589	2,019	<0.0001
CD3	563	874	1,252	812	1,108	1,479	<0.0001
CD4	327	531	850	498	705	954	<0.0001
CD8	188	320	465	264	375	525	<0.0001
CD20	44	94	282	90	144	227	<0.0001
CD4/CD8 ratio	1.2	1.7	2.6	1.3	1.9	2.6	<0.0001

* Lymphocyte subsets were performed only for patients who did not receive chemotherapy.
† Difference between median value for cases and controls.

associated with reaction to insect stings also supports earlier results (33). A possible explanation for our specific findings for allergies and for bee and wasp stings is related to people's responses to allergens and insect venom. Insect venom, particularly that of bees and wasps, initiates an inflammatory response that triggers cytokines to release histamine (36, 37). Histamine also is secreted in response to allergen exposures in atopic persons. Blood and tissue levels of histamine have been directly related to natural killer cell activity and have been inversely correlated with the presence of malignant tumors (38). In addition, the role of allergies in non-Hodgkin's lymphoma may be related to the unique ability of persons with a history of allergies to mount an immune response that requires B cells to switch immunoglobulin expression from immunoglobulin M through to immunoglobulin E.

Among women and men, the observed association with lifetime number of sexual partners was similar to the results reported in our study of non-Hodgkin's lymphoma among homosexual men (6). Seminal fluid is antigenic; in human and in animal studies, it has been shown to inhibit lymphocyte activation (39–41). Semen also is mildly immunosuppressive, and failure of its immunosuppressive activity results in the production of antibodies to semen (39–41). In men, development of serum antibodies to semen can result from exposure to their own seminal fluid because of reproductive tract trauma, infection with a sexually transmitted disease, or vasectomy (42). Divorced or never-married women had a decreased risk for non-Hodgkin's lymphoma and were more likely to have had more sexual partners, with greater exposure to the immunosuppressive effects of seminal fluid.

In the multivariate model, a reduced risk for non-Hodgkin's lymphoma was found for both women and men who had received five or more different types of vaccinations during their lifetime. We no longer observed the age-adjusted associations between risk for non-Hodgkin's lymphoma and younger age at polio vaccination among men, an effect that had remained after adjustment for several factors for HIV-negative homosexual men in our earlier report (6). Vaccines and their effects on the immune system vary, and the biologic mechanism of immune stimulation prompted by individual vaccines may be pertinent to the development of non-Hodgkin's lymphoma.

In this investigation, we tested a priori hypotheses regarding use of medications for 4 consecutive weeks or longer. In the multivariate models, a decreased risk for non-Hodgkin's lymphoma was associated with use of cholesterol-lowering drugs and use of NSAIDs (including aspirin). Initiation of an immune response requires macrophage activation and production of inflammatory mediators (43). A decreased risk for non-Hodgkin's lymphoma associated with NSAID use suggests an active role for macrophage-mediated inflammation. NSAIDs block macrophage production of B-cell growth factors, and animal models have shown that activated macrophages contribute to lymphomagenesis (43). A reduced risk for non-Hodgkin's lymphoma associated with use of pain relievers has been reported (33), and indomethacin has inhibited plasmacytoma development in mice (44). Evidence for the use of NSAIDs in reducing the risk for cancer also has come from studies of colorectal cancer (45). Similar to NSAIDs, cholesterol-lowering drugs also may decrease macrophage activation indirectly by decreasing the amount of cholesterol, a substance known to activate macrophages.

In contrast, we found that the use of cimetidine and other histamine H_2-receptor antagonists was associated with an increased risk for non-Hodgkin's lymphoma. The relation between non-Hodgkin's lymphoma and the use of drugs to treat ulcers is supportive of studies that have suggested a link between cancer and use of cimetidine or histamine H_2-receptor antagonists to treat ulcers (46, 47). Because the association was found among only those persons who had received cimetidine

and other histamine H_2-receptor antagonists, it may be that these study participants had *Helicobacter pylori*-related ulcers known to be difficult to treat with standard ulcer therapies. We did not ask about infection with *H. pylori*, but current research indicates that it is the main cause of chronic gastritis and is associated with peptic ulcer disease, gastric cancer (48), and gastric mucosa-associated lymphoid tissue lymphoma (48, 49). *H. pylori* treatment and eradication often results in the regression of mucosa-associated lymphoid tissue lymphoma (49, 50), and regression or inhibition of tumor growth in gastric cancer has been achieved with the use of some histamine H_2-receptor antagonists (46).

Regarding lifetime frequency of use among men, marijuana was the only recreational drug that remained associated with a reduced risk for non-Hodgkin's lymphoma after adjustment for potential confounding factors. Previous results examining the association between non-Hodgkin's lymphoma and recreational drug use (51) or alcohol consumption have reported no relation (51, 52). However, others have shown an increased risk among men who used recreational drugs and a decreased risk with increased consumption of alcohol among women, although confounding factors could not be excluded (53). An increased risk for non-Hodgkin's lymphoma among drinkers of beer and "mate" also has been reported (54). The use of some recreational drugs causes mild immunosuppression (55, 56), but their role in the etiology of non-Hodgkin's lymphoma is uncertain based on inconsistent results and our finding of few dose-related trends.

The relation between body mass index and risk for non-Hodgkin's lymphoma has been reported inconsistently. Similar to our results, an earlier cohort study found an increased risk with higher ponderal index (57), whereas a hospital-based study conducted in Italy found no association between body mass index and non-Hodgkin's lymphoma (58). Further investigations are needed to elucidate the significance of body mass index in the risk for non-Hodgkin's lymphoma.

Reports of the relation between common childhood and adult illnesses and non-Hodgkin's lymphoma have been inconsistent. A history of eczema (11, 33), scarlet fever (11, 35), varicella (57), herpes zoster (11, 35), pyelonephritis (35), pneumonia (11), and infectious mononucleosis (11) has been related to non-Hodgkin's lymphoma, but our results did not support these findings. Previous investigations also reported an increased risk for non-Hodgkin's lymphoma associated with diabetes mellitus (11, 59), history of blood transfusions (60, 61), organ transplants (62, 63), and autoimmune disorders such as Sjögren's syndrome (64) and rheumatoid arthritis (65), whereas risk estimates associated with a history of tonsillectomy and appendectomy have been inconsistent (35, 57, 66). We found no associations between risk for non-Hodgkin's lymphoma and any of these medical conditions. An elevated risk associated with polio in men was reported as borderline significant by another study (33). Endocrine gland disorders and splenectomy are likely to be related to overall immune system function. Splenectomy for nontraumatic reasons such as chronic platelet disorders and hemolytic anemias indicates immune system malfunction that may place these persons at greater risk for non-Hodgkin's lymphoma. However, we had no detailed information regarding splenectomy.

Lymphocyte subset analysis was performed on all blood specimens obtained from participants who had no history of recent chemotherapy. Non-Hodgkin's lymphoma patients were significantly lymphopenic, with all T- and B-cell subsets markedly decreased compared with controls. This type of shift in white blood cell count also has been observed in persons with HIV infection. The lower CD4/CD8 ratio found among the non-Hodgkin's lymphoma participants is typical of acute and chronic viral infections.

Potential for bias

We obtained our non-Hodgkin's lymphoma patients by using a rapid case ascertainment system. We used random digit dialing to obtain controls and frequency-matched them to the patients to diminish the potential effects of selection and participation biases and to increase the generalizability of results. The use of a standardized questionnaire administered in person by trained interviewers was implemented to reduce response biases.

Other potential problems such as recall bias, chance, and confounding can be inherent in this type of research, despite use of this design. The potential for recall bias may be problematic, especially when participants are asked to report events that occurred many years prior to interview or that require accurate placement of an event within a narrow time period. However, it is unlikely that cases and controls would differentially recall past exposures not perceived to be related to the disease. These forms of bias in the data are more problematic than the potential for investigators to report results due to chance (67). Response bias also can occur with the reporting of sensitive information such as sexual behavior and drug use. Drug exposures may be underreported especially by infrequent users (68, 69). In addition, inconsistencies in reported drug use may be substance dependent and influenced by increasing age (68, 69). Few subjects in our study refused to respond to personal questions, and interviewers were highly confident of the reliability of the responses.

Study size was calculated to ensure sufficient statistical power to test a priori hypotheses, and results often

were consistent with data from earlier investigations. Results based on small numbers of subjects and risk estimates with wide confidence intervals have been noted to avoid undue emphasis on these data, and they require more detailed investigation in future studies. Biologic plausibility, confounding, and effect modification also were considered when exposure effects were evaluated.

Lymphomagenesis

The findings from our study implicate environmental factors that may influence early stages of lymphomagenesis by stimulating the immune system. Antigen-driven B cells that accumulate to form lymphoma may be suppressed by immunologic stresses such as exposure to an increased number of sexual partners and to certain medications. Conversely, a history of allergies provides evidence for the persistent capacity for B-cell differentiation and therefore a decreased accumulation of B cells. The decreased risk for non-Hodgkin's lymphoma with use of NSAIDs and cholesterol-lowering drugs is consistent with a macrophage inflammatory role in B-cell proliferation and implicates the earliest stages of immune activation in lymphomagenesis. These data provide further support for immunologic activation in lymphomagenesis and, if confirmed in other work, suggest that NSAIDs and perhaps cholesterol-lowering drugs may be useful in reducing the risk for non-Hodgkin's lymphoma. Also, if B-cell lymphomas arise from a population of lymphocytes active in an immunologic response to an antigen, then sexual practices, drug use, and other behavior patterns associated with mild immunosuppression, as described in our study, may decrease the likelihood of developing non-Hodgkin's lymphoma.

The results presented here are consistent with our results regarding HIV-negative homosexual men (6) and provide additional support for the role of immune system B-cell function in lymphomagenesis. The finding of a decreased risk for cancer associated with allergy-related conditions is not unique to this study, and we have shown a consistently decreased risk for non-Hodgkin's lymphoma associated with exposures that can result in mild immunosuppression. Large studies designed to gather detailed laboratory, clinical, and epidemiologic data will best be able to elucidate the joint processes of immune function and development of non-Hodgkin's lymphoma and thereby support or refute the provocative associations reported here.

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