Specific Infections, Infection-Related Behavior, and Risk of Non-Hodgkin Lymphoma in Adults

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Abstract

Infections were examined as possible risk factors for non-Hodgkin lymphoma in a population-based case-control study in New South Wales and the Australian Capital Territory, Australia. Incident cases (n = 694) had no history of HIV infection or transplantation. Controls (n = 694) were randomly selected from electoral rolls and frequency matched to cases by age, sex, and area of residence. A postal questionnaire and telephone interview measured history of specific infections, occupational exposures, and behavioral and other risk factors for infection. Blood samples were tested for antibodies to human T-lymphotrophic virus type I and hepatitis C virus. Logistic regression models included the three matching variables and ethnicity. There was no association between risk of non-Hodgkin lymphoma and any of the variables analyzed, including sexually transmitted infections, sexual behavior, blood transfusions, influenza, acne, and either occupational or domestic exposure to zoonotic infections. Non-Hodgkin lymphoma risk was nonsignificantly elevated (odds ratio, 2.99; 95% confidence interval, 0.78-11.51) for those with a history of injecting drug use. Three cases and two controls (odds ratio, 1.32; 95% confidence interval, 0.22-7.98) tested positive to hepatitis C virus infection and none tested positive to human T-lymphotrophic virus type I/II infection. This study provides consistent evidence that sexually transmitted infections and zoonoses are not risk factors for non-Hodgkin lymphoma. (Cancer Epidemiol Biomarkers Prev 2006;15(6):1102–8)

Introduction

Non-Hodgkin lymphoma is the sixth most common cancer and cause of cancer death in Australia (1). Accepted risk factors for non-Hodgkin lymphoma are immune deficiency (2, 3) and specific infections, such as HIV, *Helicobacter pylori*, human T-lymphotrophic virus type I (HTLV-I), human herpesvirus 8, and EBV, but these account for only a small proportion of all cases, mostly rare subtypes that are uncommon in the general population. Although there is growing evidence of a positive association between the predominant B-cell non-Hodgkin lymphoma and infection with hepatitis C virus (HCV; refs. 4-6), evidence linking non-Hodgkin lymphoma and history of other specific acute and chronic infections is weak, as is the evidence linking non-Hodgkin lymphoma risk with infection-related behaviors. Possible pathogenic mechanisms include direct effects of the infectious organisms and indirect effects, such as antigen-induced inflammation.

We examined the infectious risk factors for non-Hodgkin lymphoma in adults without clinically apparent immune deficiency in a prospective, population-based case-control study in New South Wales and the Australian Capital Territory, Australia.

Materials and Methods

Subjects. Cases were prospectively identified patients with non-Hodgkin lymphoma newly diagnosed between January 2000 and August 2001, aged 20 to 74 years and resident in New South Wales or the Australian Capital Territory (7). They were notified to the population-based New South Wales Central Cancer Registry or, to minimize the time lag between diagnosis and enrollment in the study, directly to the study by high caseload clinicians. Controls were randomly selected from New South Wales and Australian Capital Territory electoral rolls (electoral enrollment is compulsory for adult Australian citizens) and frequency matched to cases by age, sex, and residential area; the intended case to control ratio was 1.

Patients with a diagnosis of chronic lymphocytic leukemia, plasma cell myeloma, precursor B and T lymphoblastic leukemia, and lymphomatoid granulomatosis grades 1 and 2 were excluded. As the study was designed to examine risk factors for non-Hodgkin lymphoma in people without obvious clinical immune deficiency, cases were excluded if they had a history of organ transplantation or HIV infection as reported by their doctor. Cases and controls with other immune conditions were not excluded. Although we did not ask for disclosure of HIV status in controls, the adult prevalence of HIV in Australia (<0.1%; ref. 8) indicated that less than one control was likely to be positive. An anatomic pathologist reviewed case pathology reports and, for some cases, original slides to assess confidence in the diagnosis of non-Hodgkin lymphoma (9).

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Data Collection

Overview. The approach to subjects and the data collection procedures were identical for cases and controls (7). Potential participants were sent a letter and information leaflet inviting their participation in research about the effects of the environment on the development of non-Hodgkin lymphoma, and verbal consent was obtained. Subjects completed a postal questionnaire and a computer-assisted telephone interview and were invited to consent to blood collection.

Data on participants' self-reported history of medical conditions were ascertained from the questionnaire and the interview. In the questionnaire, participants were presented with a list of medical conditions and asked to check those they were first diagnosed with at least 1 year before. Interviews were conducted by experienced interviewers blinded to the case and control status of participants, who interviewed similar numbers of cases and controls. Participants were asked structured questions about a range of infections in childhood (defined as the first 10 years of life) and adulthood.

Behavioral and Other Risk Factors for Infection. The questionnaire included questions on sexual experience and lifetime number of partners based on those from national sex surveys (10). In addition, personal history of specific sexually transmitted infections diagnosed at least 1 year prior, such as gonorrhea, genital herpes, genital warts, anal warts, and *Chlamydia*, was recorded.

In the questionnaire, participants recorded whether they had ever injected drugs not prescribed to them by their doctor, the age they started, and the total number of years of injecting. Participants also recorded whether they had received a blood transfusion at least 12 months before interview, their age when they first received one, and the total number they received.

Customized job-specific interview questions (''modules'') determined the participants' potential for exposure to infectious diseases transmitted from animals (zoonoses). Based on participants' occupational history in the postal questionnaire, modules were allocated by an expert occupational hygienist blinded to case-control status (11, 12). The hygienist then rated the likelihood of exposure as probable, possible, or none. Dose of exposure was calculated by combining data over all jobs in a person's entire working life. Dose was classified as substantial if the participant was probably exposed at a medium or high level for more than five 8-hour days a year for a total of >5 years and nonsubstantial for any other combination of probability, duration, and intensity of exposure.

At interview, participants were also asked about contact and frequency of contact with domestic cats or dogs as a child, teenager, and adult.

History of Specific Infections. The postal questionnaire checklist included chickenpox, genital herpes, herpes of lips (cold sores), herpes at sites other than the lips or genitals, herpes zoster (shingles), and glandular fever. Also recorded were the lifetime number of cold sore episodes, the lifetime number of shingles episodes, and the age shingles was first diagnosed.

We asked participants at interview their frequency of cold or influenza during primary school, their teenage years, and in their 20s, 30s, 40s, 50s, and 60s (as applicable). Also at interview, participants reported their frequency of acne or pimples during their teenage years, in their 20s, 30s, and 40s, and over their lifetime.

Other infectious diseases included in the questionnaire checklist were measles, otitis media, vaginal thrush, meningitis, rheumatic fever, tuberculosis, hepatitis B, HCV, other hepatitis, gastric/duodenal ulcer, diarrhea lasting >1 month, malaria, amoebic dysentery, and other tropical infectious disease.

Serology. A 10-mL blood sample was collected from each consenting participant by their doctor or a pathology laboratory venepuncturist and couriered to a central laboratory for processing and storage. Before storage, plasma samples were screened for antibodies to HTLV-I/II using an ELISA assay (GE80 HTLV-I/II enzyme immunoassay, Abbott-Murex, Abbott Park, IL), estimated to have 100% sensitivity and >99% specificity (13). After storage at −70°C for 2 to 3 years, sera were screened for HCV antibodies using a third-generation enzyme immunoassay (Cobas Core anti-HCV enzyme immunoassay II, Roche Diagnostics, Indianapolis, IN). Positive samples underwent supplementary testing for HCV antibodies using a chemiluminescence immunoassay (Vitros anti-HCV, Ortho-Clinical Diagnostics, Raritan, NJ) and then PCR (Cobas Amplicor version 2.0, Roche Diagnostics, Indianapolis, IN) for HCV RNA. Samples were defined as HCV positive if both enzyme immunoassay and chemiluminescence immunoassay tests were positive. Staff at the serology laboratories were blind to the case-control status of the samples.

Statistical Methods. Continuous variables were categorized based on the exposure distribution in controls. A priori, the following summary variables were created: one or more herpesvirus infections, one or more sexually transmitted infections, and one or more tropical infectious diseases.

Unconditional logistic regression models were adjusted for age, sex, and area. Each model also included ethnicity because fewer control subjects were born outside Australia than expected based on the 2001 Australian Census (7). To further exclude the possibility of selection bias by country of birth in controls, we also estimated associations in Australian- and New Zealand–born subjects only. Analyses were done for all cases, follicular lymphoma only (n = 227), diffuse large B-cell lymphoma only (n = 231), and mucosa-associated lymphoid tissue lymphoma of the gastrointestinal tract (n = 6).

All analyses were done using Stata software version 8.0 (Stata Corp., College Station, TX). The likelihood ratio test was used to calculate Ps for heterogeneity. Tests for linear trend were done by fitting ordered categories of a variable as a single ordinal variable in the models; trend Ps were based on the Wald test. All Ps presented are two sided, and the significance level was set at 0.05.

Results

A total of 1,217 potentially eligible cases were ascertained and 842 were approached for interview. Cases were lost after ascertainment because they had died (n = 144), could not be contacted (n = 34), or had poor English (n = 73), illness (n = 74), disability (n = 22), or immunosuppression or immune deficiency (n = 28). Of these, 717 were interviewed, for an overall participation rate of 59% and a consent rate of 85%. Twenty-three of those interviewed were excluded after pathology report (n = 13) or slide review (n = 10; these 10 cases were included in earlier reports from this study; refs. 7, 14, 15) because of low confidence in the diagnosis of non-Hodgkin lymphoma, leaving 694 cases for analysis. The majority (95%) of the included cases were of B-cell phenotype, 4% were T cell, and 1% was indeterminate. The two most common non-Hodgkin lymphoma subtypes were follicular lymphoma (33%) and diffuse large B-cell lymphoma (33%). Of the 694 cases, 597 (86%) consented to and gave a blood sample.

A total of 1,687 potentially eligible controls were randomly selected and 1,136 were approached for interview. Controls were lost after ascertainment because they had died (n = 5), could not be contacted (n = 401), or they had poor English (n = 74), illness (n = 59), or disability (n = 12). Of these, 694 were interviewed, giving a participation rate of 41% and a consent rate of 61%. A blood sample was provided by 522 (75%) of the interviewed controls.

Participating cases and controls had similar distributions by socioeconomic status and rural locality at interview (7).

Sexually Transmissible Infections. Neither lifetime number of sexual partners nor sexual behavior on the heterosexual-homosexual continuum was significantly related to non-Hodgkin lymphoma risk (Table 1). Reinforcing these results, the odds ratio [OR; 95% confidence interval (95% CI)] for 10 or more sexual partners was 1.00 (0.72-1.40), and the OR (95% CI) for any homosexual experience was 1.72 (0.74-4.00) for men. Similarly, risk of non-Hodgkin lymphoma was not significantly associated with any specific sexually transmitted infection or one or more of all such infections (Table 1).

Potential for Blood-Borne Infections. We found weak evidence of a positive association between history of injecting drug use and risk of non-Hodgkin lymphoma (OR, 2.99; 95% CI, 0.78-11.51; $P = 0.09$; Table 2). Although the number of injectors was small (eight cases, three controls), there were positive gradients in risk with decreasing age at first use ($P_{trend} = 0.11$) and increasing duration of use ($P_{trend} = 0.11$).

There was no association with receipt of any blood transfusions (Table 2). Oddly, risk was lower in those reporting two or more transfusions (OR, 0.54; 95% CI, 0.32-0.91; Table 2) than in those reporting one (OR, 1.29; 95% CI, 0.88-1.90) or none (reference category). There was also no association with age at transfusion (Table 2).

Potential for Zoonotic Infection. There was no consistent association between non-Hodgkin lymphoma risk and employment in occupations carrying a risk of zoonotic infection. At least one job with possible or probable exposure to animals was reported by 13.8% of subjects. These jobs were mainly farmers and farm hands with only a few meat workers and livestock breeders. Based on 7 cases and 1 control, the OR for *possible* exposure was raised (OR, 7.64; 95% CI, 0.94-62.36); however, that for *probable* exposure, based on 92 cases and 91 controls, was close to the null (OR, 1.05; 95% CI, 0.76-1.44). If there was additional information available and all of those with possible zoonotic exposure were classified as having probable exposure, the OR for probable exposure would have remained close to the null. Near-equal numbers of cases and controls received a non-substantial dose (OR, 1.10; 95% CI, 0.80-1.50), and two cases and no control received a substantial dose. Including potentially confounding occupational exposures, such as exposure to solvents (11) and dose of pesticides (12), did not alter the risk estimates (data not shown).

The keeping of domestic cats or dogs as a child, teenager, or adult was not predictive of non-Hodgkin lymphoma risk (ORs, 1.01, 1.06, and 0.99, respectively). This exposure was relatively common during childhood (19%), teenage years (27%), and adulthood (16%). There was also no association with amount of time spent in close contact with either cats or dogs during these years (data not shown).

Herpesvirus Infections. A history of one or more herpesvirus infections did not predict non-Hodgkin lymphoma risk (OR, 1.00; 95% CI, 0.75-1.33) nor did any of the individual herpesvirus infections we examined (Table 3). There was also no evidence of a relationship with the lifetime number of cold

Table 1. Associations of sexual behavior and self-reported history of sexually transmitted infections with non-Hodgkin lymphoma

	Cases ($n = 694$)	Controls ($n = 694$)	Adjusted OR* (95% CI)	P	P_{trend}
Sexual behavior since age 15 y					
Exclusively heterosexual	649	658	1.00		
Primarily heterosexual, some homosexual experience	9	8	1.13 (0.43-2.97)		
About equal heterosexual and homosexual experience	5	2	2.34 (0.45-12.26)		
Primarily homosexual, some heterosexual experience	3	3	1.05 (0.21-5.27)		
Exclusively homosexual	7	3	2.52 (0.65-9.80)	0.53 †	0.14 †
Never engaged in sexual activities	16	8	1.92 (0.81-4.57)		
Refused	5	12	0.34 (0.12-1.00)	0.13 ‡	—
Lifetime number of sexual partners					
1	265	273	1.00		
2-4	184	181	1.09 (0.83-1.42)		
5-9	100	91	1.18 (0.83-1.66)		
10-19	61	69	0.96 (0.64-1.43)		
20-49	36	33	1.15 (0.69-1.93)		
50-99	6	12	0.52 (0.19-1.42)		
100+	8	4	2.02 (0.59-6.88)	0.57 †	0.76 †
None	16	8	2.02 (0.84-4.85)		
Refused	18	23	0.73 (0.38-1.40)	0.40 ‡	—
Gonorrhea					
Never	682	685	1.00		
Ever	12	9	1.35 (0.56-3.24)	0.50	—
Genital herpes					
Never	682	679	1.00		
Ever	12	15	0.82 (0.38-1.77)	0.62	—
Genital warts					
Never	682	677	1.00		
Ever	12	17	0.74 (0.35-1.57)	0.43	—
Anal warts					
Never	689	691	1.00		
Ever	5	3	1.71 (0.41-7.23)	0.46	—
Chlamydia					
Never	687	691	1.00		
Ever	7	3	2.42 (0.62-9.47)	0.18	—
One or more of above sexually transmitted infections					
Never	654	651	1.00		
Ever	40	43	0.95 (0.61-1.49)	0.83	—

*Adjusted for the matching variables (age, sex, and geographic area) and ethnicity.
†P, excluding subjects who refused to answer or never engaged in sexual activities.
‡P, including all subjects.

Table 2. Potential for exposure to blood-borne infections and non-Hodgkin lymphoma

	Cases (n = 694)	Controls (n = 694)	Adjusted OR* (95% CI)	$P_{heterogeneity}$	P_{trend}
Injecting drug use					
Never	686	691	1.00		
Ever	8	3	2.99 (0.78-11.51)	0.09	—
Age first injected drugs					
Never	686	691	1.00		
>20 y	2	1	2.26 (0.20-25.10)		
≤20 y	6	2	3.37 (0.66-17.04)	0.23	0.11
No. years injected					
None	686	691	1.00		
≤3	4	2	2.25 (0.41-12.49)		
>3	4	1	4.47 (0.49-40.58)	0.21	0.11
Blood transfusion †					
Never	601	595	1.00		
Ever	91	95	0.95 (0.69-1.30)	0.73	—
Do not know	2	4			
Number of blood transfusions †					
None	601	595	1.00		
One	68	52	1.29 (0.88-1.90)		
Two or more	23	42	0.54 (0.32-0.91)	0.02	0.21
Do not know ‡	2	5			
Age first blood transfusion †					
Never	601	595	1.00		
≥35 y	51	47	1.04 (0.68-1.60)		
<35 y	40	47	0.87 (0.56-1.36)	0.81	0.65
Do not know ‡	2	5			

*Adjusted for the matching variables (age as a continuous variable, sex, and geographic area) and ethnicity.
†At least 1 year before interview.
‡One control subject recalled having a blood transfusion but could not recall their age or the number of transfusions; the remainder of subjects in this category did not know whether they had received a blood transfusion.

sore or shingles episodes or the age shingles was first diagnosed (data not shown).

Cold or Influenza. Risk of non-Hodgkin lymphoma was not significantly associated with history of cold or influenza during any of the life periods examined (data not shown). This exposure occurred for 5% of participants during primary school and 11% during adulthood.

Acne or Pimples. The ORs for a history of acne at any age as well as acne severity were all close to unity (data not shown). A history of acne was experienced by 38% of participants at some time during their lifetime.

Other Infectious Diseases. None of the remaining infectious diseases we examined were significantly associated with risk of non-Hodgkin lymphoma (Table 4); a history of vaginal thrush approached significance (OR, 0.77; 95% CI, 0.54-1.08). The ORs were raised for history of tuberculosis and history of HCV, and restricting to B-cell lymphomas raised the OR (95% CI) for HCV a little to 1.59 (0.50-5.05). A history of gastric or duodenal ulcer, indicative of probable infection by *H. pylori*, was reported by 67 (10%) controls and 3 (50%) gastric mucosa-associated lymphoid tissue lymphoma cases (OR, 10.77; 95% CI, 1.99-58.27).

Serology. None of the blood samples tested positive for antibodies to HTLV-I/II.

Blood sample volume was insufficient to conduct all three HCV tests for nine cases and four controls. Samples from five subjects (three cases, two controls) tested positive to the enzyme immunoassay and chemiluminescence immunoassay HCV antibody tests (OR, 1.32; 95% CI, 0.22-7.98). Restricting to B-cell lymphomas raised the OR slightly (OR, 1.41; 95% CI, 0.23-8.56). All but one of these samples (one control) also tested positive to HCV RNA. Of the four cases and four controls to report a history of HCV infection at interview and give a blood sample, only two cases tested HCV positive. Of the four cases and two controls to report a history of injecting drug use and give a blood sample, three cases and one control tested HCV positive. Four of the five HCV-positive participants had a history of injecting drug use.

Study Population Subgroups. Our results were not appreciably altered when the analyses were restricted to Australian- and New Zealand–born subjects, follicular lymphomas, or diffuse large B-cell lymphomas (data not shown).

Discussion

In this population-based study of non-Hodgkin lymphoma in adults without clinically apparent immune deficiency or HIV infection, detailed indices of exposure to sexually transmitted infections and zoonoses were consistently not related to non-Hodgkin lymphoma risk. There was some evidence that a history of injecting drug use, but not blood transfusion, was

Table 3. Associations of self-reported history of herpesvirus infections and non-Hodgkin lymphoma

	Cases (n = 694)	Controls (n = 694)	Adjusted OR* (95% CI)	$P_{heterogeneity}$
Chickenpox				
Never	216	191	1.00	
Ever	478	503	0.90 (0.71-1.15)	0.41
Genital herpes				
Never	682	679	1.00	
Ever	12	15	0.82 (0.38-1.77)	0.62
Herpes of lips (cold sores)				
Never	414	417	1.00	
Ever	280	277	1.04 (0.84-1.29)	0.73
Herpes at sites other than genitals or lips				
Never	679	684	1.00	
Ever	15	10	1.53 (0.68-3.45)	0.30
Herpes zoster (shingles)				
Never	620	621	1.00	
Ever	74	73	1.02 (0.72-1.44)	0.91
Infectious mononucleosis (glandular fever)				
Never	625	626	1.00	
Ever	69	68	1.07 (0.75-1.53)	0.72

*Adjusted for the matching variables (age as a continuous variable, sex, and geographic area) and ethnicity.

related to non-Hodgkin lymphoma risk. The most likely candidate blood-borne pathogen is HCV, and 80% of those testing positive for HCV had a history of injecting drug use. HCV serology was only weakly supportive of a positive association with non-Hodgkin lymphoma risk. No cases or controls tested positive to HTLV-I/II. None of the other self-reported infectious diseases we examined were significantly associated with risk of non-Hodgkin lymphoma.

One sexually transmitted infection, HIV, is associated with greatly increased risk of non-Hodgkin lymphoma. Risk is associated with the degree of immunodeficiency and chronic B-cell stimulation (16). Whether other sexually transmitted infections are associated with non-Hodgkin lymphoma is unknown. In our HIV-negative population, we found no evidence of an association between non-Hodgkin lymphoma and sexual behavior or self-reported history of sexually transmitted infections. There have been very few studies of this question. One study in a HIV-positive population reported no association with sexually transmitted infections (17), but others have produced conflicting results possibly due to confounding by HIV infection (18, 19). Only one study tested for serologic evidence of a sexually transmitted infection (20); this small hospital-based case-control study showed a significant positive association between non-Hodgkin lymphoma and *Chlamydia trachomatis* antibodies detected by ELISA but not when the more specific microimmunofluorescence method was used.

Previous population-based data on the association with injecting drug use are limited and inconsistent (19, 21, 22). In our HIV-negative population, we found elevated but nonsignificant risks for history and duration of injecting drug use; we speculate that this is due to HCV infection. Alternative explanations are direct immune-related effects of the injected substances or as yet unrecognized blood-borne infectious agents. The absence of a positive association with blood transfusions both in our data and the bulk of the literature (23) argues against the latter. HCV is the most prevalent blood-borne virus in injecting drug use in Australia, and 80% of those living with HCV acquired it through injecting drug use (24). Our data concur with this estimate, as four of the five HCV-positive participants reported a history of injecting drug use.

Although we did not find a statistically significant association with serologically confirmed HCV infection, our point estimate was consistent with those from other low HCV prevalence countries (4). Moreover, the HCV prevalence in our controls (0.4%; median age, 58 years; interquartile range, 50-67 years) was in good agreement with a recent Australian national seroprevalence estimate for ≥50-year-olds (0.7%; ref. 25). Recent population-based data from large incident case series in the United States (5, 6) and a systematic review (4) support a positive association between HCV infection and non-Hodgkin lymphoma risk.

HTLV-I is a human retrovirus strongly associated with the development of adult T-cell leukemias (26). The absence of HTLV-I antibodies in any of our participants is consistent with the lack of any adult T-cell leukemias in our cases and the very low prevalence of HTLV-I in Australian blood donors (27).

Using state-of-the-art occupational exposure assessment methods, we found no evidence of an association between occupational exposure to risk of zoonotic infection and non-Hodgkin lymphoma risk. However, we had limited statistical power to detect an association with substantial exposures, as only two cases and no control had this level of exposure. This is the first population-based study to examine occupational exposure to animals directly, having previously been approached only indirectly by assuming animal exposure in certain jobs. For example, although it is generally accepted that agricultural workers have increased risks of non-Hodgkin lymphoma (28), not all agricultural workers have exposure to animals and farmers are exposed to other potential carcinogens, including pesticides and other chemicals. Studies of farmers' exposure to specific animal species have not produced consistent results (29-31), and risks of non-Hodgkin lymphoma for workers in more specifically animal-related industries have not been consistently increased (32, 33). Thus, the evidence for an association between occupational risk of zoonotic infection and non-Hodgkin lymphoma risk remains weak. We also found no evidence that the keeping of domestic cats or dogs is associated with non-Hodgkin lymphoma risk, corroborating previous studies (29, 31, 34, 35).

There is compelling evidence that some herpesviruses are etiologic agents in specific lymphoid and epithelial tissue cancers. The association between infection with EBV and Hodgkin's lymphoma, Burkitt's lymphoma, and natural killer-T lymphomas is regarded as causal (36). In the immune

Table 4. Associations of self-reported infectious disease history with non-Hodgkin lymphoma

	Cases (n = 694)	Controls (n = 694)	Adjusted OR* (95% CI)	$P_{heterogeneity}$
Measles				
Never	167	154	1.00	
Ever	527	540	1.03 (0.79-1.34)	0.83
Otitis media				
Never	513	517	1.00	
Ever	181	177	1.07 (0.84-1.37)	0.58
Vaginal thrush (women)				
Never	175	159	1.00	
Ever	115	138	0.77 (0.54-1.08)	0.13
Rheumatic fever				
Never	670	674	1.00	
Ever	24	20	1.24 (0.68-2.27)	0.49
Meningitis				
Never	684	681	1.00	
Ever	10	13	0.78 (0.34-1.81)	0.57
Tuberculosis				
Never	686	690	1.00	
Ever	8	4	1.86 (0.55-6.29)	0.30
Hepatitis B				
Never	684	682	1.00	
Ever	10	12	0.80 (0.34-1.88)	0.61
Hepatitis C				
Never	687	689	1.00	
Ever	7	5	1.48 (0.47-4.72)	0.50
Other hepatitis				
Never	660	662	1.00	
Ever	34	32	1.07 (0.65-1.77)	0.78
Gastric or duodenal ulcer				
Never	636	627	1.00	
Ever	58	67	0.84 (0.58-1.22)	0.37
Diarrhea lasting >1 month				
Never	675	675	1.00	
Ever	19	19	1.02 (0.53-1.96)	0.95
Malaria				
Never	678	683	1.00	
Ever	16	11	1.40 (0.64-3.07)	0.39
Amoebic dysentery				
Never	690	688	1.00	
Ever	4	6	0.66 (0.18-2.37)	0.52
Other tropical infectious disease†				
Never	686	682	1.00	
Ever	7	11	0.60 (0.23-1.57)	0.29
One or more tropical infectious disease‡				
Never	669	666	1.00	
Ever	24	28	0.81 (0.46-1.43)	0.47

*Adjusted for the matching variables (age as a continuous variable, sex, and geographic area) and ethnicity.

†Excluding one case and one control who gave nonspecific descriptions of the disease.

‡Malaria, amoebic dysentery, or other tropical infectious disease (mainly dengue virus and Ross River virus), including one control who reported malaria and another nonspecific tropical disease and excluding one case who reported a nonspecific tropical disease only.

deficient, human herpesvirus 8 infection is associated with a rare B-cell non-Hodgkin lymphoma (37) and EBV infection is associated with non-Hodgkin lymphoma (38). Herpesvirus infections are typically chronic and recurrent, theoretically providing an important source of antigenic stimulation. In our study, self-reported history of infectious mononucleosis, a condition caused by delayed exposure to EBV, was not associated with non-Hodgkin lymphoma risk nor were any of the other herpesvirus infections we examined.

Other investigations of the association between non-Hodgkin lymphoma and antecedent herpesvirus infection have produced inconsistent but generally null results. Three studies reported a significant positive association with history of herpes zoster (39-41), whereas five studies found no association (42-46). Only one (39) of four (19, 44, 47) prior studies to examine non-Hodgkin lymphoma risk with herpes simplex infection or cold sores reported a positive association.

Our finding of no association between non-Hodgkin lymphoma and the predominantly childhood infections is consistent with all previous studies of chickenpox (31, 40, 41, 46) and all but one (31) previous study of measles (18, 40, 41, 48). Positive associations with other childhood infections, such as scarlet fever (39, 40), varicella (48), and diphtheria (39), have been inconsistently reported, although there are no prior reports of positive associations with history of mumps, rubella, whooping cough, or pertussis.

We found no significant association between history of cold or influenza and non-Hodgkin lymphoma risk. This result agrees with all but one prior study (44) examining these or related illnesses (39-41, 43, 46, 48). Our finding of no association with acne at any stage of life also concurs with the only prior evidence (44).

We found no significant associations with a range of other specific infections, although the low numbers of people reporting many of the infections we examined limited our capacity to examine them. In coherence with the majority of prior studies, non-Hodgkin lymphoma risk was elevated for those with a history of tuberculosis (39-41, 43, 44, 47, 49, 50). Arguing against a pathogenic role for chronic infection per se, no other bacterial or viral infection apart from tuberculosis and HCV has consistently been associated with risk of non-Hodgkin lymphoma in the nonimmune deficient.

This was a large, prospective, population-based study with non-Hodgkin lymphoma diagnosis confirmed by pathology report and slide review. Rapid case ascertainment minimized survival bias and the case participation rate was reasonably high. However, the relatively low response rate in controls raises the possibility of selection bias if cases' and controls' decisions to participate were differentially affected by their infectious disease history.

We used structured questionnaires and trained interviewers blinded to case-control status. Because most exposure classifications were based on recall, misclassification is possible. As very little is known about the etiology of non-Hodgkin lymphoma, however, it should be nondifferential. Such misclassification would bias results toward the null and may partially account for the pattern of null results we observed. It is also possible that we had nondifferential underreporting of high-risk behaviors, such as certain sexual behaviors and injecting drug use. However, the high proportion of injecting drug use with confirmed HCV infection adds to the credibility of our injecting drug use exposure assessment.

In summary, we found no strong evidence for an association between any infection and non-Hodgkin lymphoma risk in immunocompetent people. In particular, we found consistent evidence that sexually transmitted infections and zoonoses are not risk factors for non-Hodgkin lymphoma. Risk did increase, however, with injecting drug use and our results are compatible with other results, suggesting that HCV infection increases non-Hodgkin lymphoma risk. Taken together with previous findings, we think it is unlikely that infection per se has any major effect on risk of non-Hodgkin lymphoma in the immunocompetent population.

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