American Journal of Epidemiology
Vol. 157, No. 6
Printed in U.S.A.
DOI: 10.1093/aje/kwg004

Prescription Medications Associated with a Decreased Risk of Non-Hodgkin's Lymphoma

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Received for publication January 18, 2002; accepted for publication September 30, 2002.

Earlier epidemiologic studies have suggested an inverse association between non-Hodgkin's lymphoma and exposure to histamine$_2$ (H_2) blockers, nonsteroidal anti-inflammatory drugs, cholesterol-lowering drugs, and antibiotics. Data from the PHARMO database were used to conduct a nested, population-based case-control study that included 1985–1998 drug-dispensing records for 300,000 residents of six Dutch cities. Included were those subjects without a previous history of cancer who were aged ≥20 years and were registered with an incident primary discharge diagnosis of non-Hodgkin's lymphoma between 1991 and 1998. This paper includes data on 211 cases and 800 controls individually matched on sex, age, community pharmacy, calendar time, and duration of follow-up. Conditional logistic regression analysis was used to evaluate the association between non-Hodgkin's lymphoma and categories of cumulative drug use in days. In multivariate analyses, nonsignificant risk reductions were found for all drugs tested, and the negative association tended to increase with increasing duration of use. For women, the odds ratio for H_2 blockers was 0.29 (95% confidence interval: 0.12, 0.69) and for analgesics was 0.40 (95% confidence interval: 0.22, 0.71). Results support an inverse association between occurrence of non-Hodgkin's lymphoma and use of H_2 blockers and analgesics among women, and they warrant confirmation in larger studies.

antibiotics; anticholesteremic agents; anti-inflammatory agents, non-steroidal; histamine agents; lymphoma, non-Hodgkin; pharmacoepidemiology

Abbreviations: H_2, histamine$_2$; ICD-9-CM, *International Classification of Diseases*, Ninth Revision, Clinical Modification; NSAID, nonsteroidal anti-inflammatory drug.

Non-Hodgkin's lymphoma includes a group of different hematologic neoplasms that originate from T and B cells in the lymphatic system (1). In the Netherlands, the 1997 rate of non-Hodgkin's lymphoma per 100,000 person-years was reported as 10.3 in men and 7.2 in women (2). A steady, but consistent increase in the incidence of lymphoma has been observed worldwide (3). Currently, little is known about risk factors for the disease, although immunodeficiency diseases such as acquired immunodeficiency syndrome, autoimmune conditions such as rheumatoid arthritis, and viral diseases are among the factors that have been associated with an increased risk of non-Hodgkin's lymphoma (4–7). Moreover, drugs such as phenytoin and chemotherapy have been associated with an increased risk of non-Hodgkin's lymphoma (8, 9).

A recent population-based case-control study that investigated a variety of risk factors for non-Hodgkin's lymphoma suggested that some medications may reduce the risk of this disease (10). Although most results were statistically significant in this study, use of nonsteroidal anti-inflammatory drugs (NSAIDs), histamine$_2$ (H_2) blockers, antibiotics, and cholesterol-lowering drugs was associated with a reduced

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risk of non-Hodgkin's lymphoma. These findings were somewhat consistent with those from earlier cohort (7, 11–14) and case-control (4, 8, 15) studies. However, several studies have reported antibiotics, H_2 blockers, NSAIDs, analgesics (4, 15), and cholesterol-lowering drugs to be associated with a reduced risk of non-Hodgkin's lymphoma. However, drug exposure was assessed differently in these studies. In studies of transplant patients, exposure assessment was based on medical records (7, 8, 13); in most other studies, drug exposure was ascertained through interview data (4, 15, 16).

Our objective was to study the potential negative association between non-Hodgkin's lymphoma and exposure to H_2 blockers, NSAIDs and analgesics, cholesterol-lowering drugs, and antibiotics. To this end, we used automated dispensing data since they are gathered prospectively and reduce some forms of potential bias (17).

MATERIALS AND METHODS

Setting

Data were derived from the PHARMO record linkage system, a database that contains the drug-dispensing records from community pharmacies and hospital discharge records of a defined population of approximately 300,000 residents of the Netherlands (18). In this geographic area, all admissions and all pharmacy data are registered. Because almost all persons designate a single pharmacy to fill their prescriptions from general practitioners or medical specialists, dispensing histories are virtually complete. For all subjects, the drug-dispensing histories were linked to hospital discharge records with a probabilistic algorithm based on patient characteristics such as date of birth, gender, and general practitioner. Validation of a set of 9,822 records demonstrated that both sensitivity and specificity of this linkage exceeded 95 percent (19). The hospital records included detailed information concerning primary and secondary diagnoses, procedures, and dates of admission and discharge. All diagnoses were coded according to the *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM).

The study period was January 1, 1985, to January 1, 1999. Participants in the PHARMO population entered the database when their first prescription was filled in a PHARMO community pharmacy, and they were followed until their last prescription was filled.

Selection of cases and controls

In this nested, population-based case-control study, cases included all subjects ≥20 years of age who were registered with an incident primary discharge diagnosis of non-Hodgkin's lymphoma (ICD-9-CM codes 200 and 202) between January 1, 1991, and December 31, 1998. If available, the non-Hodgkin's lymphoma diagnosis was validated by using morphologic and procedure codes provided by biopsy and other detailed examination. In the source population of PHARMO, 251 patients with a primary discharge diagnosis of non-Hodgkin's lymphoma were identified. Forty patients had a history of cancer or chemotherapy before the diagnosis of non-Hodgkin's lymphoma and were excluded from the study because of an increased baseline risk of cancer recurrence.

A total of 800 controls were individually matched to the final 211 non-Hodgkin's lymphoma cases. Because we assumed a potential latent period of 1 year between induction of non-Hodgkin's lymphoma and diagnosis of the malignancy, the index date was calculated by subtracting 1 year from the date of diagnosis. All patients with a history of malignant cancer and radiotherapy in the baseline period between January 1, 1985, and January 1, 1991, were excluded. Furthermore, we excluded all persons who had a diagnosis of human immunodeficiency virus–related disease during the study period.

Controls were sampled from person-time contributed by subjects in the PHARMO population who never had been discharged with a primary or secondary code for non-Hodgkin's lymphoma, cancer, or radiotherapy; who had not filled prescriptions for anticancer drugs; and who were part of the PHARMO population on the index date of the case. For every case, four controls were matched by sex, year of birth, community pharmacy, calendar period, and duration of follow-up in PHARMO within 6-month periods. In every matched set, cases and controls had the same index date.

Exposure assessment

The pharmacy records in the PHARMO database contained automated information on all dispensed prescriptions and included the product name, international nonproprietary name, ATC code (20), number of tablets/capsules or other dosage forms, date of delivery, prescribed daily number, dosage, and prescribed length of drug therapy. Exposure initially was defined as ever/never use of antibiotics, H_2 blockers, NSAIDs and analgesics, and cholesterol-lowering drugs prior to the index date. In a second step, we assessed intermittent or consecutive cumulative exposure until the index date. Because the time since last exposure may be important, we assessed cumulative exposure by subtracting 3 and 5 years from the date of diagnosis. This step also was done to reduce any risk of protopathic bias, because drug use might change during the prodromal period of non-Hodgkin's lymphoma.

Potential confounders

We created a comorbidity indicator by searching for any diagnosis in the hospital records coded according to ICD-9-CM that contained conditions previously associated with non-Hodgkin's lymphoma, including heart failure, rheumatoid arthritis, systemic lupus erythematosus, embolism and thrombosis, hemorrhage, pneumonia, decubitus ulcer, anemia, and elevated sedimentation rate. Furthermore, as a proxy of comorbidity, we investigated the potentially confounding effects of number of prior hospitalizations and number of pharmacy visits and filled prescriptions during the 1 year prior to the index date.

Analysis

To compare proportions, we used χ^2 statistics or Fisher's exact test whenever the expected cell counts were less than 5. All statistical tests were two sided, with a rejection of the null hypothesis at $p < 0.05$. Conditional logistic regression analysis was used to evaluate associations between ever drug use or categories of cumulative drug use in days and risk of non-Hodgkin's lymphoma. Odds ratios as estimates of the relative risk were computed, and duration-response relations were tested for trend with categories of increasing exposure duration. Effect modification by age and sex was investigated by testing for interactions between exposures and sex or age in the categories <55, 55–70, and >70 years, respectively.

RESULTS

The baseline characteristics of the 211 cases and 800 matched controls are listed in table 1. The overall number of hospital admissions prior to the index date, defined as 1 year before the date of diagnosis, was similar for cases and controls. The comorbidity indicator was more prevalent in non-Hodgkin's lymphoma patients (9 percent) than in controls (4 percent), $p < 0.01$.

The total number of prescriptions was significantly lower for cases than controls. Although cases and controls were matched on index date and duration of their presence in the PHARMO population until the date of diagnosis, controls were present in PHARMO for a longer period. The median follow-up period for PHARMO cases and controls was 2,462 and 2,762 days, respectively. Therefore, all analyses were adjusted for follow-up time in days.

Table 2 presents the odds ratios for the association between non-Hodgkin's lymphoma and ever exposure to the drug classes of H_2 blockers, cholesterol-lowering drugs, antibiotics, NSAIDs, and analgesics 1 year prior to the date of hospital admission for non-Hodgkin's lymphoma. All investigated medications were associated with a lower risk of the disease relative to nonuse, but adjustment for the comorbidity indicator and follow-up time in days moved the risk estimates toward unity, and many confidence limits also overlapped 1.0. Adjustment for other factors did not change the point estimates. Of the 211 cases, only one was exposed to cholesterol-lowering drugs compared with 53 controls. Several selected drug exposures also were stratified by duration of use. For H_2 blockers, use for more than 2 years was associated with an 87 percent lower risk compared with no use. An elevated risk was associated with proton-pump inhibitors (odds ratio = 2.1, 95 percent confidence interval: 0.33, 13.3) after cumulative use of more than 2 years. For antibiotics, cumulative use for longer than 3 months was associated with a risk reduction of 51 percent after adjustment for other factors. Cumulative NSAID use generally was shorter than 2 years (54 of the 59 cases). Further categorization within the 2-year class did not reveal heterogeneity of risk.

Exposure to analgesics was associated with a lowered risk of non-Hodgkin's lymphoma (table 3). Gender was a significant effect modifier, with reduced risks of non-Hodgkin's lymphoma associated with H_2 blockers and analgesics among women. Use of these medications did not alter the risk of non-Hodgkin's lymphoma among men. Stratification for age had no effect on the risk estimate (data not shown).

We also considered lag time for medication use to exclude use related to possible symptoms of non-Hodgkin's lymphoma. The protective effects of ever use remained when we used index dates that were 3 and 5 years before the date of diagnosis. Cumulative use of H_2 blockers up to an index date 3 years before the diagnosis of non-Hodgkin's lymphoma was associated with a significant risk reduction of 48 percent. Similarly, cumulative use of analgesics up to an index date that was 5 years before the date of diagnosis yielded a significant risk reduction of 39 percent (table 4).

DISCUSSION

In this study, we found nonsignificant reductions in the risk of non-Hodgkin's lymphoma with exposure to H_2 blockers, cholesterol-lowering drugs, antibiotics, NSAIDs, and analgesics. However, the decreased risks generally were stronger with increasing cumulative duration of use. These effects were not always entirely consistent over categories of duration of use and lag periods. A significant negative association was observed for exposure to H_2 blockers and analgesics only in women but not in men.

Our findings on the association of drug use and the occurrence of non-Hodgkin's lymphoma are supported by other studies (10, 15). A large study investigating medication use suggested a negative association with NSAIDs and serum-lipid-lowering drugs (10) but reported results that differed from ours regarding the effect of H_2 blockers. In the earlier study (10), an increased risk with cimetidine was noted, although the exposure was much less common than in our study, that is, less than 1 percent.

An increased risk of non-Hodgkin's lymphoma was found with the use of NSAIDs when long-term regular use of aspirin was included together with other pain relievers and antacids (4, 15). In all studies mentioned, the exposure assessment was based on interview data using a retrospective case-control design. Variations in risk by sex have been reported in other studies as well as ours, with an increased risk of non-Hodgkin's lymphoma observed for use of digitalis in women and for vaccinations in men (15). The increased risk with the H_2 blocker cimetidine was predominately present among women (10). Similarly, the odds ratios for H_2 blockers were 1.8 for men (10) and 1.2 in our study, albeit not significant

The underlying mechanisms of a protective effect of prescription medications on non-Hodgkin's lymphoma are mainly unknown. However, it has been suggested that immune-competent cells play an important role because an association exists between non-Hodgkin's lymphoma and immunodeficiency diseases such as acquired immunodeficiency syndrome, autoimmune diseases such as rheumatoid arthritis, and viral diseases such as infectious mononucleosis. Immune-competent cells such as Th1 and Th2 play a role in lymphomagenesis (10, 21, 22). Any effect of drugs on these cells might theoretically influence the risk of non-Hodgkin's lymphoma. Beta-lactam antibiotics, for instance, have an influence on Th1 (23). We found a decreased risk of

TABLE 1. Characteristics of non-Hodgkin's lymphoma cases and controls according to hospitalization data from the PHARMO database, the Netherlands, 1985–1998

Characteristic	Cases (n = 211)		Controls (n = 800)		p value
	No.	%*	No.	%*	
Age (years)†					
20–29	16	8	63	8	
30–39	10	5	39	5	
40–49	23	11	92	12	
50–59	43	20	158	20	
60–69	50	24	189	24	
70–79	52	25	198	25	
≥80	17	8	61	8	
Sex					
Women	101	48	372	46	
Men	110	52	428	53	
Duration of registration in PHARMO (years) prior to the date of diagnosis of non-Hodgkin's lymphoma or the index date for controls					
0 to ≤1	11	5	3	0.4	
>1 to ≤3	19	9	36	5	
>3 to ≤5	44	21	158	20	
>5 to ≤7	38	18	123	15	
>7 to ≤9	53	25	245	31	
>9	46	22	235	29	<0.001
Presence of comorbidity indicator‡	18	9	32	4	0.01
Prior no. of pharmacy visits					
0–4	71	34	203	25	
5–18	61	29	199	25	
19–45	44	21	197	25	
>45	35	17	201	25	0.01
Prior no. of overall prescriptions§					
0–22	94	36	164	21	
23–59	37	18	208	26	
60–142	45	21	210	26	
>142	35	17	218	27	<0.001

* Some percentages do not total 100 because of rounding.

† Mean, 59.7; standard deviation, 16.4.

‡ Combined variable included conditions such as heart failure, embolism/thrombosis, hemorrhage, pneumonia, decubitus ulcer, anemia, and elevated sedimentation rate.

§ Mean, 107; standard deviation, 129.

non-Hodgkin's lymphoma associated with antibiotics, especially after repeated use that exceeded a cumulative period of 9 months. The cytokine balance between Th1 and Th2 is influenced by the estrogen-androgen ratio, and we found results to vary by sex. NSAIDs inhibit the macrophage-initiated immune response (24–26). In animal models and observational etiologic studies, a potential anticancer effect of NSAIDs was attributed to the inhibition of the two isoforms of the enzyme cyclooxygenase (26).

Almost 40 percent of all non-Hodgkin's lymphomas are extranodal, and 25 percent of the primary extranodal lymphomas affect the stomach (27–29), for example, mucosa-associated lymphoid tissue lymphoma. The strongest risk reduction was seen after cumulative use of H_2 blockers for 2 years or more, possibly by protecting the mucosa-associated lymphoid tissue. We did not find the same reduced risk with proton-pump inhibitors. Because prodromal symptoms might have changed the prescription

TABLE 2. Associations between non-Hodgkin's lymphoma and various prescription medications used at least 1 year prior to the index date, PHARMO population, the Netherlands, 1985–1998

Exposure	Cases (n = 211)		Controls (n = 800)		Crude OR*	95% CI*	Adjusted OR†	95% CI
	No.	%	No.	%				
Histamine$_2$ blockers								
Ever	28	13	155	19	0.60	0.39, 0.94	0.68	0.41, 1.41
<730 days	27	13	120	15	0.76	0.05, 1.21	0.86	0.50, 1.46
≥730 days	1	0.5	35	4	0.09	0.01, 0.67	0.13	0.02, 1.00
Cholesterol-lowering drugs								
Ever	1		53	7	0.03	0.002, 0.56		
Antibiotics								
Ever	131	62	586	73	0.53	0.37, 0.76	0.81	0.51, 1.26
<10 days	36	17	164	21	0.53	0.34, 0.85	0.72	0.40, 1.29
10–90 days	85	40	337	42	0.60	0.40, 0.88	0.93	0.57, 1.50
>90 days	10	5	85	11	0.27	0.13, 0.56	0.49	0.22, 1.11
NSAIDs*								
Ever	124	59	567	71	0.52	0.37, 0.73	0.89	0.58, 1.37
<730 days	114	54	534	67	0.51	0.36, 0.73	0.89	0.58, 1.36
≥730 days	10	5	33	4	0.65	0.30,1.43	1.02	0.38, 2.74
Analgesics								
Ever	109	52	497	62	0.61	0.44, 0.84	0.74	0.50, 1.11
<30 days	61	29	241	30	0.71	0.49, 1.03	0.85	0.53, 1.34
30–730 days	43	20	227	28	0.50	0.33, 0.77	0.65	0.39, 1.07
>730 days	5	2	29	4	0.44	0.16, 1.19	0.55	0.17, 1.75

* OR, odds ratio; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs.
† Adjusted for comorbidity indicator (refer to the text) and follow-up time (in days) as continuous variables.

for H_2 blockers, we investigated the use with 3- and 5-year lag periods. H_2 blockers were associated with a reduced risk with a 3-year lag period but not with a 5-year lag period. The role of cholesterol-lowering drugs in the etiology of cancer remains controversial (30). The negative association of cholesterol-lowering drugs may be mediated by inhibition of the bioactivation of mutated ras proteins, because mutations of these proteins are found in 30 percent of human tumors (31–33). The risk reduction of more than 90 percent found in our study should be interpreted with caution; exposure was low in both cases and controls, and we were unable to examine the role of duration of use and lag periods. However, the reduced risk of non-Hodgkin's lymphoma we found, in conjunction with earlier reports (10), warrants further research on the role of cholesterol-lowering drugs and cancer.

The strengths of our study were its population-based design; adjustment for confounding factors such as age, sex, and calendar time; and detailed information on drug exposure over a 9-year period. The availability of these data

TABLE 3. Associations between non-Hodgkin's lymphoma and selected prescription medications, stratified by sex, PHARMO population, the Netherlands, 1985–1998

Factor	Women				Men			
	Cases (no.) (n = 101)	Controls (no.) (n = 372)	OR*,†	95% CI*	Cases (no.) (n = 110)	Controls (no.) (n = 428)	OR†	95% CI
Histamine$_2$ blockers	7	80	0.29	0.12, 0.69	21	75	1.20	0.61, 2.34
Antibiotics	64	281	0.82	0.44, 1.55	67	305	0.81	0.42, 1.57
NSAIDs*	57	277	0.70	0.38, 1.27	67	290	0.98	0.52, 1.85
Analgesics	45	250	0.40	0.22, 0.71	64	247	1.27	0.70, 2.32

* OR, odds ratio; CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs.
† Adjusted for comorbidity indicator and follow-up time (in days) as continuous variables.

TABLE 4. Associations between non-Hodgkin's lymphoma and various drug exposures, considering a lag period of exposure, PHARMO population, the Netherlands, 1985–1998

Exposure (ever use of)	Cases (n = 211)		Controls (n = 800)		Crude OR*	95% CI*	Adjusted OR†	95% CI
	No.	%	No.	%				
Histamine$_2$ blockers								
3-year lag	19	9	115	14	0.55	0.33, 0.94	0.52	0.27, 0.97
5-year lag	11	5	65	8	0.58	0.30, 1.15	0.68	0.31, 1.50
Antibiotics								
3-year lag	102	48	480	60	0.53	0.37, 0.75	0.80	0.52, 1.23
5-year lag	71	34	354	44	0.51	0.35, 0.74	0.88	0.54, 1.43
NSAIDs*								
3-year lag	91	43	478	60	0.42	0.30, 0.59	0.72	0.48, 1.10
5-year lag	57	27	346	43	0.37	0.25, 0.54	0.68	0.43, 1.07
Analgesics								
3-year lag	80	38	427	53	0.45	0.32, 0.64	0.67	0.45, 1.01
5-year lag	52	25	310	39	0.40	0.27, 0.59	0.61	0.38, 0.98

* OR, odds ratio; CI, confidence interval.; NSAIDs, nonsteroidal anti-inflammatory drugs.
† Adjusted for comorbidity indicator and follow-up time (in days) as continuous variables.

enabled us to calculate various levels and categories of exposure to prescription medications. Because data on drug use were gathered prior to disease onset, and because little is known about drug-associated non-Hodgkin's lymphoma, it is unlikely that information bias invalidated our results.

Hospitalizations for conditions that have been associated with non-Hodgkin's lymphoma were combined in a summary indicator, and number of days of follow-up was adjusted for in the analysis (4, 5, 9, 13, 34–36). Study limitations included no available data on other risk factors or risk indicators such as lifestyle, smoking, body mass index, nutrition, or occupation that might have confounded our results (14, 16, 34, 37–42). The lack of data on over-the-counter medication use of special importance for NSAIDs and analgesics might have led to underestimation of exposure. However, there is no reason to expect that this underestimation would have differed between cases and controls. Moreover, because all prescription drugs are free of charge in the Netherlands, little incentive exists for chronic users to obtain over-the-counter NSAIDs and analgesics. A second limitation is the relatively small number of non-Hodgkin's lymphoma patients in the PHARMO catchment area and the fact that we could not verify the discharge diagnosis by using original medical charts. Moreover, we had to rely on the ICD-9-CM codes registered as hospital discharge diagnosis, as has been done previously (43). Nevertheless, we expect that misclassification of the disease would have been small because non-Hodgkin's lymphoma is not diagnosed without pathologic data. Our results support an inverse association between use of H_2 blockers, NSAIDs, analgesics, cholesterol-lowering drugs, and antibiotics and occurrence of non-Hodgkin's lymphoma and warrant confirmation in larger studies.

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