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Aspirin and other nonsteroidal anti-inflammatory drugs, statins and risk of non-Hodgkin lymphoma

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Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) and statin drugs may protect against the development of non-Hodgkin lymphoma (NHL), but data are limited, particularly for NHL subtypes. Furthermore, some in vitro, animal and epidemiologic data suggest there may be a synergistic effect of these two agents, but there has been no test of this hypothesis in NHL. We evaluated the self-reported use of NSAIDs and statins in a clinic-based study of 1703 NHL patients and 2199 frequency-matched controls. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for potential confounding variables. We observed an inverse association of regular use of low-dose aspirin with risk of NHL (OR = 0.82; 95% CI 0.70–0.96) that was stronger with longer duration of use ($P < .01$). There were no associations for use of regular or extra-strength aspirin, ibuprofen, other NSAIDs, statins or other cholesterol-lowering drugs with NHL risk, while an inverse association with COX-2 inhibitors was equivocal. There was also no interaction of low-dose aspirin and statins on NHL risk. Inverse associations of similar magnitude to all NHL were observed for regular use of low-dose aspirin with diffuse large B-cell, follicular, marginal zone and all other lymphomas, although not all associations were statistically significant. In conclusion, low-dose aspirin but not regular/extra strength aspirin, other NSAIDs or statin use was associated with lower risk of NHL. Beyond

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available on request from the corresponding author.

the potential for the primary prevention of NHL, these data also point to a role of anti-platelet or other effects of low-dose aspirin in lymphomagenesis that warrant follow-up.

Keywords

aspirin; non-Hodgkin lymphoma; prevention; statins

1 | INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies with an estimated 81 560 new cases and 20 720 deaths in the United States in 2021.[1] Although our understanding of the etiology of NHL remains incomplete, risk has been consistently associated with chronic inflammation related to infections, autoimmune disease and other chronic disease processes.[2] Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), as well as statin drugs, are known to reduce levels of inflammation. These drugs are widely used, often chronically, and thus are attractive classes of medications to evaluate in the prevention of cancer. Indeed, the United States Preventive Services Task Force (USPSTF) recommended (Grade B) initiating low-dose aspirin (81 mg/d) for the primary prevention of cardiovascular disease (CVD) and colorectal cancer in adults aged 50 to 59 years who have a 10% or greater 10-year risk of CVD, have a least at 10-year life expectancy and are not at increased risk of bleeding; a Grade C was given for adults aged 60 to 69 years, and evidence was considered incomplete for adults of other ages.[3] This was the first USPSTF recommendation for a pharmacologic agent for cancer chemoprevention in a population not characterized as having a high risk of developing cancer.[4]

Evidence for a role of aspirin, other NSAIDs and statins in the etiology of NHL is still emerging. In a meta-analysis of 17 studies (12 case-control and 5 cohort studies) in adults, neither the use of aspirin (odds ratio [OR] = 1.02, 95% confidence interval [CI] 0.89–1.17) nor nonaspirin NSAIDs (OR = 1.26, 95% CI 0.86–1.85) were associated with NHL risk, although aspirin use was protective for CLL/SLL (OR = 0.70, 95% CI 0.54–0.91) and nonaspirin NSAIDs use was associated with NHL risk in women (OR = 1.41, 95% CI 1.01–1.97).[5] In a meta-analysis of 10 studies (5 case-control, 4 cohort and 1 randomized trial), statin use was inversely associated with overall NHL risk (OR = 0.82, 95% CI 0.69–0.99); an inverse association was also observed for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and T-cell lymphoma, but was only statistically significant for marginal zone lymphoma (MZL; OR = 0.54, 95% CI 0.31–0.94).[6] Of particular note, however, excluding statin use within one year of diagnosis attenuated the association with NHL risk (OR = 0.92, 95% CI 0.80–1.06).

We present data from a large case-control study on the association of aspirin, other NSAIDs, and statins with risk of NHL. We were able to assess details of use, adjust for potential confounding factors and systematically test for subtype-specific associations for the major NHL subtypes. Furthermore, we assessed the joint effects of NSAIDs and statins on risk,

which is of interest as there is some evidence of a synergistic effect of statins and NSAIDs as a combination regimen for cancer chemoprevention.[7]

2 | METHODS

2.1 | Study population

We have previously published full details of this clinic-based, case-control study conducted at the Mayo Clinic (Rochester, MN).[8] Briefly, we prospectively offered enrollment to all consecutive cases of pathologically confirmed lymphoma, including CLL/SLL and Hodgkin lymphoma (HL), who were age 18 years and older; a resident of Minnesota, Iowa or Wisconsin at the time of diagnosis; within 9 months of initial diagnosis enrollment; and without a history of lymphoma, leukemia or HIV/AIDS. A Mayo Clinic hematopathologist reviewed materials for each case to verify the diagnosis and to classify each case according to the WHO Classification of Neoplastic Diseases of the Hematopoietic and Lymphoid Tissues.[9] Of the 3844 eligible cases identified from 1 September 2002 through 31 December 2012, 2640 (68.7%) participated, 447 (11.6%) refused, 73 (1.9%) were unreachable (ie, we were unable to contact them after multiple attempts) and 684 (17.8%) failed to consent within 9 months of diagnosis or despite consenting failed to complete the protocol within 12 months of diagnosis. We excluded 219 cases with a diagnosis of HL, leaving 2421 cases.

We enrolled clinic-based controls from Mayo Clinic Rochester patients who had prescheduled general medical examinations (ie, not a diagnostic examination for a specific, active symptom or new disease) in the Department of Medicine. Controls were eligible if they had no history of lymphoma, leukemia or HIV/AIDS; were age 18 years or older; and a resident of Minnesota, Iowa or Wisconsin at the time of appointment. We used a computer program to randomly select controls, frequency matched to cases based on the marginal distribution of 5-year age group, sex and geographic location of residence (based on distance from Rochester, Minnesota and urban/rural status). Of the 4222 eligible controls identified from 1 September 2002 through 31 December 2012, 2430 (57.6%) participated, 1372 (32.5%) refused and 420 (9.9%) failed to consent within 9 months of selection or despite consenting failed to complete the protocol within 12 months of selection.

2.2 | Exposure assessment

We used a self-administered questionnaire provided at enrollment to collect information on demographic characteristics, family history of cancer, anthropometrics, medical history (including history of rheumatoid arthritis [RA] and osteoarthritis [OA]), as well as selected lifestyle and other factors. We collected data on use of statin cholesterol-lowering drugs and other cholesterol-lowering drugs, excluding use in the last 2 years, as well as age at first use and number of years used. We also asked participants “excluding the last two years, did you regularly take any of the following medications? (exclude use of less than once per month)” for baby or low-dose aspirin (162 mg or less); regular strength aspirin (163 mg or more, eg, Bufferin, Anacin, Bayer, Excedrin, Ecotrin, etc.); ibuprofen (eg, Motrin, Advil, Nuprin, Medipin, etc.); other anti-inflammatory analgesics (eg, Naprosyn, Anaprox, Aleve, Voltaren, Feldene, Toradol, Indocin, etc.); and COX-2 inhibitors (eg, Celebrex, Vioxx, etc.). For each yes response, we then inquired about average days per month used; on days used, the

number of pills taken; and the total number of years taken. For each drug, we defined a user as someone who reported use at least four times per month for at least 1 year; a nonuser was defined as no or infrequent use (less than four times per month). Average number of pills per week was defined as the average number of days per month used multiplied by the number of pills taken on days used, then divided by 4. Pill-years were defined as the average number of pills per day multiplied by years of use. As virtually all low-dose aspirin users reported one pill per day, we did not calculate pill-years for this exposure.

The NSAIDs questions were updated in 2004 and the older version could not be harmonized. After excluding these participants, there were 1703 NHL cases (64.5%) and 2199 controls (90.5%) available for analysis. Participants (cases and controls combined) with NSAIDs data were more likely to be female (44.6% vs 36.7%), slightly older (mean age 61.7 vs 59.5 years) and residents of Minnesota (74.6% vs 68.6%), but had a similar distribution by NHL subtype. These modest differences suggest a relatively small potential for selection bias, and as noted below, all models were adjusted for age, gender and residence.

2.3 | Statistical analysis

We used unconditional logistic regression to estimate ORs and corresponding 95% CIs for the association of medication use with risk of NHL, adjusting for the design variables of age at enrollment, sex and residence. A *P*-trend was calculated in unconditional logistic regression models using the ordinal scoring of the increasing exposure categories with the no use as the reference category. We considered a nominal $P < .05$ as statistically significant. We evaluated potential confounding first by adding education level and year of first registration at Mayo to the basic model, and second by further adding family history of NHL in a first degree relative, body mass index (BMI in kg/m^2, and grouped into WHO categories), smoking (pack-years), alcohol use (never, former, current use) and history of RA or OA to the model. We also conducted sensitivity analyses stratified on gender, BMI (<25 vs 25+ kg/m^2), smoking status (ever vs never), and history of RA or OA (ever vs never).

We assessed subtype associations using polytomous logistic regression[10] to simultaneously model a comparison between the control group with each of the five NHL subtypes—CLL/SLL, DLBCL, follicular lymphoma, MZL and one group that included all of the other (less common) subtypes combined. We used a 4 df Wald test to assess heterogeneity across the subtypes, and a $P < .05$ was considered statistically significant. All analyses were conducted using SAS software system (SAS Institute, Cary, NC; version 9.4).

3 | RESULTS

The mean age of cases was 61.8 years and 59% were male, while the mean age of controls was 61.6 years and 53% were male (Table 1). All participants resided in Minnesota, Iowa or Wisconsin, and 75% had some education after high school, slightly higher in controls. Compared to controls, cases had a slightly higher BMI, family history of NHL and had ever smoked cigarettes. Alcohol use and history of RA were similar between cases and controls while history of OA was somewhat more common in controls. The most common NHL

subtype was CLL/SLL (N = 495), followed by follicular lymphoma (N = 410), DLBCL (N = 326) and MZL (N = 134).

Use of regular or extra-strength aspirin (16.6% of cases and 16.0% of controls) was not associated with risk of NHL in the basic model that adjusted for study design variables (age, sex and residence), or after adjusting for education and time in the Mayo system or other potential NHL confounders (Table 2). In contrast, we observed an inverse association of low-dose aspirin use (28.5% of cases and 34.9% of controls) with risk of NHL (OR = 0.74; 95% CI 0.64–0.85), with a stronger association for longer duration of use in the basic model (Table 2). These associations were similar or slightly stronger after adjusting for education and year of first registration at Mayo, suggesting that these variables were unlikely to be major confounders. After further adjustment for family history of NHL, BMI, smoking, alcohol use and history of RA, the inverse associations attenuated slightly (eg, OR = 0.82 for regular use of low-dose aspirin; 95% CI 0.70–0.96) but remained statistically significant.

While a test for heterogeneity for the associations of low-dose aspirin use by gender was not statistically significant ($P = .28$), the inverse association with NHL was stronger in females (OR = 0.71, 95% CI 0.55–0.92) than males, where it was attenuated and was not statistically significant (OR = 0.89, 95% CI 0.73–1.10). In males, duration of low-dose aspirin use did show an inverse trend, but this was not statistically significant and it was weaker than the duration trend in females (Table 3).

We next evaluated the association of low-dose aspirin use with NHL risk in selected subgroups. The inverse association with NHL was observed in those with a BMI of <25 kg/m^2 (OR = 0.80, 95% CI 0.59–1.08) and ≥25 kg/m^2 (OR = 0.82, 95% CI 0.68–0.99) and in ever smokers (OR = 0.81, 95% CI 0.65–1.03) and never smokers (OR = 0.82, 95% CI 0.66–1.02). In analyses stratified on history of either OA or RA, any regular low-dose aspirin use was inversely associated with NHL in those with no history (OR = 0.79, 95% CI 0.65–0.94) but was attenuated in those with any history (OR = 0.92, 95% CI 0.66–1.27). B symptoms, which include fever, night sweats and weight loss, are not infrequent in NHL patients up to 6 months before diagnosis and could lead to use of antipyretics potentially leading to reverse causation or recall bias of earlier use. However, respondents excluded use in the two years before diagnosis, and when we excluded cases with B symptoms (N = 546) the inverse association with low-dose aspirin use remained (OR = 0.78, 95% CI 0.65–0.92).

For low-dose aspirin, the strongest inverse trends were observed for DLBCL and all other subtypes, followed by follicular lymphoma, and MZL, while there were no consistent associations for CLL/SLL (Table 4). However, the test for heterogeneity by NHL subtype was not statistically significant.

We did not observe an association with ibuprofen use (19.0% of cases and 17.9% of controls) but did observe inverse associations for other NSAIDs (5.6% of cases and 8.5% of controls; OR = 0.66; 95% CI 0.51–0.87) and for COX-2 inhibitors (5.0% of cases and 7.9% of controls; OR = 0.59; 95% CI 0.45–0.79) (Table 2). The latter associations attenuated after adjustment for education, length of time registered in the Mayo and other NHL risk factors, with only ever use of COX-2 inhibitors (OR = 0.70; 95% CI 0.51–0.96) but not use of other

NSAIDs (OR = 0.78, 95% CI 0.58–1.05) remaining statistically significant. However, neither of these drug classes showed consistent trends with the duration of use or pill-years. These findings were largely consistent across subgroup analyses based on BMI, smoking and history of RA or OA, although they were stronger in men for use of other NSAIDs and stronger in women for use of COX-2 inhibitors (Table 3). In analysis by NHL subtypes, inverse associations for COX-2 inhibitors were strongest for follicular lymphoma and CLL/SLL, although the number of exposed cases was small and the test of heterogeneity by subtype was not statistically significant (Table 4). Use of ibuprofen or other nonaspirin NSAIDs was not associated with any of the NHL subtypes (Table 4).

Use of statins (32.4% of cases and 35.5% of controls) or other cholesterol-lowering drugs (6.4% of cases and 7.4% of controls) were not associated with NHL risk overall (Table 5) or in subtypes analysis (Table 4). When we modeled the joint use of low-dose aspirin and statins, the strongest inverse association was observed for low-dose aspirin use only, followed by use of both aspirin and statins; there was no association with statin use only and no evidence for any interaction of aspirin and statins on risk (Table 5). There were also null associations for a similar analysis modeling the joint use of regular or extra strength aspirin and statins with risk of NHL.

4 | DISCUSSION

The most robust result from this large, clinic-based case-control study was an inverse association of regular, sustained use of low-dose aspirin (≤162 mg/d) with NHL risk, with evidence for a stronger association with longer duration of use. These results did not appear to be confounded by education, year of first registration at Mayo or other NHL risk factors, and were observed for all major NHL subtypes except CLL/SLL, although not all were statistically significant. The inverse associations were stronger in women but still apparent, although not statistically significant, in men. In contrast, there was no evidence of associations for regular or extra-strength aspirin or ibuprofen, while inverse associations with COX-2 inhibitors or other nonaspirin NSAIDs attenuated after adjustment for potential confounding factors. There was no evidence of statins, alone or in combination with aspirin use, associated with NHL risk.

Strengths of our study included the large sample size; careful selection of the control group for the clinic-based cases; central pathology review to determine NHL subtypes; relatively detailed assessment of use of aspirin, other NSAIDs and statins; a comprehensive assessment of confounding and effect modification; and evaluation of NHL subtype-specific associations. We previously reported our control selection for this clinic-based case-control study had strong internal validity as well as external validity, including replication of major associations in the literature and risk factor distributions for controls comparable to population-based data.[8]

Limitations included self-report of all exposures, which lead to misclassification of unknown extent. Nondifferential misclassification of exposures would likely lead to lower study power. Differential recall bias by cases vs controls is also a possibility given that cases have a stronger incentive to ruminate on prior exposures, although these exposures are relatively

recent in the epidemiologic literature, and one would hypothesize reporting of any aspirin use, not just low-dose aspirin, would have been subject to this potential bias. Also, B symptoms (fever, night sweats, and weight loss in the 6 months before diagnosis) affect 10% to 30% of NHL patients (varying by subtype) and could lead to increased use of antipyretics and the potential for differential recall bias of these agents. However, B symptoms occur within 6 months of diagnosis, and respondents were asked to exclude use in the two years before diagnosis and further, when we excluded cases with B symptoms our findings did not change.

Reverse causality is another potential bias with our study design, although we focused on regular, long-term use, which would not be expected to impact the associations with long-term low-dose aspirin use. Of more concern for the low-dose aspirin association is potential confounding by socioeconomic status and access or use of preventive health care. However, adjustment for education and year of first registration at Mayo if anything slightly strengthened the associations, although these variables are rather weak surrogates for these factors. Finally, the study population was almost exclusively white, and thus these results may not generalize to other racial/ethnic groups.

A meta-analysis[5] of 17 studies (12 case-control and 5 cohort studies) found that the use of any aspirin (OR = 1.02, 95% CI 0.89–1.17) was not associated with overall NHL risk, and there was no evidence of effect medication by a variety of factors, including gender, study design (case-control vs cohort), source population (general population vs other), geographic region (USA vs other) and drug and confounder information source (administrative database vs other). No results were available for low-dose aspirin use. Furthermore, in the meta-analysis,[5] aspirin use was not associated with DLBCL or follicular lymphoma, consistent with our results, but was inversely associated with CLL/SLL (OR = 0.70; 95% CI 0.54–0.91), which we did not observe. The latter finding was based on four studies[11–14] with a total of 777 CLL/SLL cases compared to 495 cases our study.

The same meta-analysis[5] also reported a positive association for use of nonaspirin NSAIDs with overall NHL risk (OR = 1.33, 95% CI 1.11–1.60), which was stronger in females (OR = 1.41, 95% CI 1.01–1.96) than males (OR = 1.16, 95% CI 0.84–1.61). There were no significant associations for DLBCL, follicular or CLL/SLL, although data were limited. In contrast, we did not observe any associations with use of ibuprofen and although we did observe an inverse association with other nonaspirin NSAIDs, this association attenuated after adjustment for potential confounding factors and did not show consistent trends with duration of use and pill-years. An inverse association with use of COX-2 inhibitors did remain after adjustment, but there were no consistent trends with pills per day, duration of use, or pill-years. A population-based case-control study found an increased risk of regular use of COX-2 inhibitors with NHL risk (OR = 1.58, 95% CI 0.68–3.67),[15] but was based on only three exposed cases. A nested case-control study from a primary care database found that regular use of COX-2 inhibitors for more than a year was associated with an increased risk of lymphoma (OR = 1.21, 95% CI 1.01–1.45), with greater risk for long-term use (OR = 1.70, 95% CI 1.21–2.40).[16] Given the limited data, more studies will be needed to understand any potential association with COX-2 inhibitors in NHL.

Few studies have reported on low-dose aspirin use with NHL risk. Consistent with our results, the VITAL cohort (N = 235 NHL cases) showed a suggestive inverse association of low-dose aspirin use (HR = 0.75 for ≥4 days/week for ≥4 years vs no regular use, 95% CI 0.49–1.15) but not regular dose aspirin use (HR = 1.17, 95% CI 0.80–1.71).[13] No results for NHL subtypes were available. In contrast, a Dutch population-based study[17] that linked pharmacy data on long-term low-dose (≤100 mg/d) aspirin use with cancer registry data found no association with lymphoma (N = 256 cases; HR = 1.34 for >6 years duration vs no use, 95% CI 0.74–2.43); the specific subtypes included in the lymphoma group were not reported, nor were any NHL subtype specific results. Secondary analyses of randomized cardiovascular trials provide some evidence that daily aspirin use reduces the incidence of all cancers combined, cancer mortality and distant metastases, even at low doses (75–100 mg/d).[18,19] In a pooled analysis of data on nonfatal and fatal cancers from 32 randomized controlled trials in primary prevention of vascular events, aspirin use was inversely associated with hematologic malignancies for 0 to 3 years (OR = 0.79, 95% CI 0.49–1.27) and >3 years (OR = 0.86, 95% CI 0.53–1.40) after randomization, although neither estimate was statistically significant.[20] Across all follow-up, lymphoma incidence was reduced (25 vs 45 cases, $P = .017$; no OR reported). Thus, while these limited data are somewhat supportive of a protective effect of low-dose aspirin, clearly more data are needed.

Dose and duration of aspirin use are closely related to the intended clinical impact, ranging from 75 mg (antiplatelet) to 325 to 600 mg (analgesic) to 1.2 g (anti-inflammatory) per day. Our results implicate low-dose aspirin use and thus point to antiplatelet effects. At low doses, aspirin irreversibly inhibits COX-1 (via acetylation) but has little impact on COX-2 until higher doses. NSAIDs reversibly block COX-1 and COX-2, with COX-2 inhibitors selective for COX-2.[21] COX-1 and COX-2 convert arachidonic acid into prostaglandins, thromboxanes and prostacyclins, and COX-1 is constitutively expressed in most tissues while COX-2 expression is induced by inflammation, wound healing and neoplasia. Our results add to a small but accumulating literature in support of the hypothesis that inhibition of platelet activation by low-dose aspirin may have both cardioprotective and anti-cancer effects, with the latter effects linked to impacts on pathways related to proliferation, apoptosis, angiogenesis and immune evasion.[22] Furthermore, our results suggest that higher-dose aspirin, ibuprofen and statins, drugs that reduce inflammation (among other biologic effects), do not appear to lower lymphoma risk even though sustained inflammation seems to raise it overall or for certain NHL subtypes, although there was some, albeit weak, evidence of a potential protective effect of other nonaspirin NSAIDs beyond ibuprofen and COX-2 inhibitors.

A meta-analysis of 10 studies[6] found that statin use was inversely associated with NHL risk overall (OR = 0.82, 95% CI 0.69–0.99) and for several NHL subtypes (only statistically significant for MZL), and results were consistent by study design (cohort vs case-control studies) and source population (general population vs hospital-based). However, the overall association attenuated after excluding statin use within one year of diagnosis (OR = 0.92, 95% CI 0.80–1.06). Our results, which excluded use in the 2 years before diagnosis, did not find any evidence for an overall association with NHL or any of the common NHL subtypes, consistent with the latter finding. A recent large, population-based case-control study (5541 cases including multiple myeloma and 27 315 controls) found an inverse association with

ever use of a statin (excluding use 1 year before diagnosis) with risk of all NHL after adjustment for other medications and healthcare utilization (OR = 0.82, 95% CI 0.76–0.89), but no clear association with dose or duration of use. In analyses by subtype, inverse associations were observed for DLBCL, multiple myeloma, and other B-cell NHL. In secondary analysis, the association appeared to be restricted to high potency statin and lipophilic statins.[23] Our study could not address the type of statin used. Furthermore, we did not find any associations with other cholesterol lowering drugs. Serum cholesterol, high-density lipoprotein and low-density lipoprotein levels were found to be lower in lymphoma cases compared to controls in the 10 years before diagnosis, most pronounced 3 to 4 years before diagnosis,[24] suggesting that low cholesterol levels could be a preclinical marker of lymphoma and introduce bias if not excluding exposures before diagnosis of lymphoma. We also did not observe an interaction of statin use with aspirin, as hypothesized based mainly from laboratory data or human data from studies of gastrointestinal cancers.[7]

5 | CONCLUSION

In summary, our study supports the concept that regular use of aspirin at a dose that is able to inhibit platelet activity but does little to suppress inflammation reduces the likelihood of developing NHL, while use of higher dose aspirin, other NSAIDs or statins does not. Larger multi-institutional studies would be helpful to confirm this finding, along with mechanistic studies of low-dose aspirin in the context of lymphomagenesis.

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Abbreviations:

BMI	body mass index
CI	confidence intervals
CLL	chronic lymphocytic leukemia
CVD	cardiovascular disease
DLBCL	diffuse large B-cell lymphoma
HL	Hodgkin lymphoma
MZL	marginal zone lymphoma
NHL	non-Hodgkin lymphoma
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
OR	odds ratio

RA	rheumatoid arthritis
SLL	small lymphocytic lymphoma
USPSTF	United States Preventive Services Task Force

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What's new

Non-steroidal anti-inflammatory drugs (NSAIDs) and statin drugs may protect against the development of non-Hodgkin lymphoma, but data are limited, particularly for subtypes of the disease. In this large case-control study, regular use of low-dose aspirin was inversely associated with risk of non-Hodgkin lymphoma and most non-Hodgkin lymphoma subtypes. There was no association with use of regular/extra-strength aspirin, ibuprofen, other NSAIDs, or cholesterol-lowering drugs. Beyond the potential of low-dose aspirin in the primary prevention of non-Hodgkin lymphoma, these data point to a role of anti-platelet or other effects of low-dose aspirin in lymphomagenesis that warrants follow-up.

TABLE 1

Participant characteristics, Mayo Clinic Case-Control Study of NHL, 2002–2012

	Controls (N = 2199)		Cases (N = 1703)	
Characteristic	**N**	**%**	**N**	**%**
Age group				
≤40	144	6.5	98	5.8
41–50	257	11.7	223	13.1
51–55	234	10.6	183	10.7
56–60	236	10.7	221	13.0
61–65	382	17.4	276	16.2
66–70	349	15.9	242	14.2
71–75	305	13.9	207	12.2
>75	292	13.3	253	14.9
Age in years, mean (SD)	61.6	(13.2)	61.8	(13.1)
Sex				
Male	1164	52.9	998	58.6
Female	1035	47.1	705	41.4
State of residence				
Iowa	266	12.1	314	18.4
Minnesota	1736	78.9	1175	69.0
Wisconsin	197	9.0	214	12.6
Highest education level				
Less than high school graduate	56	2.6	87	5.1
High school graduate	448	20.4	372	21.9
Some college/vocational school	594	27.1	515	30.4
College graduated	465	21.2	340	20.0
Graduate or professional school	631	28.8	382	22.5
Missing	5		7	
BMl 2 years ago	27.8	5.3	28.3	5.3
Family history of NHL				
No	1954	92.0	1419	86.9
Yes	170	8.0	213	13.1
Missing	75		71	
Smoking history				
Never	1235	56.4	884	52.2
Former	841	38.4	710	41.9
Current	113	5.1	101	5.9
Missing	10		8	
Alcohol history				
Never	208	9.5	200	11.8
Former	307	14.0	292	17.2
Current	1673	76.1	1201	70.5

	Controls (N = 2199)		Cases (N = 1703)	
Characteristic	**N**	**%**	**N**	**%**
Missing	11		10	
Rheumatoid arthritis				
No	1990	94.8	1537	93.6
Yes	110	5.2	105	6.4
Missing	99		61	
Osteoarthritis				
No	1607	78.0	1379	84.9
Yes	454	22.0	245	15.1
Missing	138		79	

TABLE 2

Association of aspirin and other NSAIDs use with NHL risk, Mayo Clinic Case-Control Study, 2002–2012

			Basic model[a]		Basic + SES[b]		Basic + confounders[c]	
Regular use of agent	**Controls**	**Cases**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Regular or extra strength aspirin								
Nonuser	1808	1398	1.00	Reference	1.00	Reference	1.00	Reference
User[d]	344	279	0.99	(0.83, 1.19)	0.99	(0.82, 1.20)	1.00	(0.82, 1.22)
Pills per week								
≤7	171	148	1.06	(0.84, 1.35)	1.05	(0.82, 1.35)	1.00	(0.77, 1.30)
>7	166	125	0.91	(0.71, 1.17)	0.91	(0.70, 1.20)	1.00	(0.76, 1.32)
P-trend			.67		.67		.98	
Duration of use, years								
<5	69	54	0.99	(0.68, 1.44)	1.01	(0.68, 1.51)	0.98	(0.64, 1.49)
5–9	61	51	1.00	(0.67, 1.48)	1.10	(0.73, 1.67)	1.17	(0.76, 1.79)
10 or more	214	174	0.99	(0.80, 1.24)	0.95	(0.75, 1.20)	0.97	(0.76, 1.23)
P-trend			.94		.81		.95	
Pill-years								
≤6.0	110	99	1.10	(0.82, 1.47)	1.07	(0.78, 1.46)	1.11	(0.80, 1.53)
6.1–15.0	116	89	0.94	(0.70, 1.26)	0.99	(0.72, 1.35)	0.90	(0.65, 1.24)
>15.0	111	85	0.93	(0.69, 1.26)	0.90	(0.65, 1.24)	1.00	(0.71, 1.40)
P-trend			.66		.64		.83	
Low dose aspirin								
Nonuser	1409	1187	1.00	Reference	1.00	Reference	1.00	Reference
User[d]	754	472	0.74	(0.64, 0.85)	0.73	(0.62, 0.85)	0.82	(0.70, 0.96)
Duration of use, years								
<5	218	138	0.74	(0.59, 0.94)	0.74	(0.57, 0.94)	0.83	(0.64, 1.07)
5–9	224	157	0.81	(0.64, 1.01)	0.79	(0.62, 1.01)	0.92	(0.72, 1.19)
10 or more	312	177	0.69	(0.56, 0.85)	0.68	(0.54, 0.84)	0.73	(0.58, 0.92)
P-trend			.000080		.000087		.0091	
Ibuprofen								
Nonuser	1776	1350	1.00	Reference	1.00	Reference	1.00	Reference

			Basic model[a]		Basic + SES[b]		Basic + confounders[c]	
Regular use of agent	**Controls**	**Cases**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
User[d]	386	317	1.08	(0.91, 1.28)	1.09	(0.91, 1.30)	1.11	(0.92, 1.35)
Pills per week								
≤7	40	32	1.09	(0.67, 1.77)	1.22	(0.73, 2.04)	1.10	(0.65, 1.87)
>7	343	281	1.07	(0.90, 1.28)	1.07	(0.88, 1.29)	1.11	(0.91, 1.35)
P-trend			.42		.44		.29	
Duration of use, years								
<5	103	73	0.89	(0.65, 1.23)	0.89	(0.64, 1.25)	0.99	(0.69, 1.42)
5–9	84	69	1.07	(0.76, 1.49)	1.14	(0.80, 1.63)	1.12	(0.77, 1.63)
10+	199	175	1.18	(0.95, 1.48)	1.17	(0.92, 1.48)	1.17	(0.92, 1.49)
P-trend			.17		.19		.19	
Pill-years								
≤5.0	138	102	0.94	(0.71, 1.24)	0.98	(0.73, 1.31)	1.00	(0.74, 1.35)
5.1–13.3	124	107	1.19	(0.90, 1.57)	1.23	(0.92, 1.64)	1.24	(0.92, 1.68)
>13.3	121	104	1.11	(0.84, 1.48)	1.06	(0.79, 1.43)	1.10	(0.80, 1.51)
P-trend			.26		.33		.24	
Other anti-inflammatory NSAIDs (eg, Naprosyn, Anaprox, Aleve, Voltaren, Feldene, Toradol, Indocin, etc.)								
Nonuser	1987	1572	1.00	Reference	1.00	Reference	1.00	Reference
User[d]	184	94	0.66	(0.51, 0.87)	0.70	(0.53, 0.93)	0.78	(0.58, 1.05)
Pills per week								
≤7	55	33	0.87	(0.55, 1.38)	0.98	(0.61, 1.58)	1.13	(0.68, 1.89)
>7	127	60	0.59	(0.42, 0.81)	0.60	(0.43, 0.85)	0.68	(0.48, 0.97)
P-trend			.0013		.0063		.062	
Duration of use, years								
<5	85	44	0.67	(0.46, 0.99)	0.69	(0.46, 1.03)	0.77	(0.50, 1.18)
5–9	38	22	0.75	(0.43, 1.30)	0.90	(0.50, 1.63)	0.95	(0.52, 1.73)
10+	61	28	0.60	(0.37, 0.95)	0.61	(0.37, 1.00)	0.70	(0.43, 1.17)
P-trend			.0045		.019		.12	
Pill-years								
≤2.6	66	31	0.63	(0.40, 0.98)	0.68	(0.42, 1.09)	0.79	(0.48, 1.30)

			Basic model[a]		Basic + SES[b]		Basic + confounders[c]	
Regular use of agent	**Controls**	**Cases**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
2.7–8.0	62	28	0.58	(0.37, 0.93)	0.59	(0.36, 0.96)	0.67	(0.41, 1.11)
>8.0	53	34	0.82	(0.52, 1.30)	0.91	(0.56, 1.48)	0.99	(0.60, 1.63)
P-trend			.017		.065		.27	
COX-2 inhibitors								
Nonuser	2000	1586	1.00	Reference	1.00	Reference	1.00	Reference
User[d]	171	83	0.59	(0.45, 0.79)	0.66	(0.49, 0.89)	0.70	(0.51, 0.96)
Pills per week								
≤7	127	61	0.59	(0.43, 0.82)	0.65	(0.46, 0.91)	0.62	(0.43, 0.90)
>7	43	20	0.55	(0.32, 0.95)	0.65	(0.36, 1.17)	0.92	(0.50, 1.68)
P-trend			.00029		.0073		.065	
Duration of use, years								
<5	123	58	0.55	(0.40, 0.76)	0.61	(0.43, 0.87)	0.60	(0.41, 0.87)
5–9	27	16	0.79	(0.42, 1.50)	0.81	(0.41, 1.59)	1.32	(0.65, 2.68)
10+	21	9	0.63	(0.28, 1.41)	0.80	(0.35, 1.81)	0.72	(0.30, 1.74)
P-trend			.0031		.036		.14	
Pill-years								
≤2.0	71	42	0.68	(0.45, 1.01)	0.79	(0.52, 1.20)	0.75	(0.47, 1.18)
2.1–5.0	52	15	0.37	(0.20, 0.67)	0.38	(0.20, 0.71)	0.33	(0.17, 0.67)
>5.0	47	24	0.66	(0.40, 1.10)	0.74	(0.43, 1.26)	1.09	(0.62, 1.92)
P-trend			.00045		.0060		.070	

[a] Adjusted for age, sex and residence.

[b] Further adjusted for education and year of first registration at Mayo.

[c] Further adjusted for education, family history of lymphoma, BMI, smoking history, alcohol use, RA and osteoarthritis.

[d] A user is defined as someone who reported use as least once per week for at least one year.

TABLE 3

Association of low dose aspirin, other NSAIDs and COX-2 inhibitor use with risk of NHL by gender, Mayo Clinic Case-Control Study, 2002–2012[a]

	Females				Males			
	Controls	**Cases**	**Odds ratio**	**95% CI**	**Controls**	**Cases**	**Odds ratio**	**95% CI**
Low dose aspirin								
Nonuser	590	465	1.00	Reference	606	546	1.00	Reference
User[b]	258	128	0.71	(0.55, 0.92)	365	277	0.89	(0.73, 1.10)
Duration of use, years								
<5	88	45	0.73	(0.49, 1.09)	89	74	0.92	(0.65, 1.30)
5–9	75	43	0.78	(0.51, 1.18)	111	95	1.03	(0.75, 1.40)
10 or more	95	40	0.64	(0.42, 0.96)	165	108	0.79	(0.59, 1.04)
P-trend			.012				.17	
Other anti-inflammatory NSAIDs (eg, Naprosyn, Anaprox, Aleve, Voltaren, Feldene, Toradol, Indocin, etc.)								
Nonuser	757	545	1.00	Reference	912	794	1.00	Reference
User[b]	86	47	0.86	(0.58, 1.28)	67	38	0.70	(0.46, 1.09)
Pills per week								
≤7	28	15	0.96	(0.48, 1.91)	16	14	1.42	(0.65, 3.08)
>1	57	32	0.83	(0.51, 1.34)	50	24	0.55	(0.32, 0.92)
P-trend			.45				.055	
Duration of use, years								
<5	46	21	0.66	(0.38, 1.17)	24	17	0.95	(0.48, 1.86)
5–9	17	10	1.13	(0.48, 2.65)	15	11	0.82	(0.36, 1.89)
10 or more	23	16	1.07	(0.54, 2.13)	28	10	0.44	(0.20, 0.94)
P-trend			.87				.042	
Pill-years								
≤2.6	30	14	0.75	(0.37, 1.49)	21	13	0.84	(0.40, 1.75)
2.7–8.0	36	14	0.56	(0.28, 1.09)	19	13	0.87	(0.41, 1.84)
>8.0	19	19	1.71	(0.85, 3.42)	25	12	0.54	(0.26, 1.14)
P-trend			.99				.11	
COX-2 inhibitors								
Nonuser	761	560	1.00	Reference	927	797	1.00	Reference

	Females				Males			
	Controls	**Cases**	**Odds ratio**	**95% CI**	**Controls**	**Cases**	**Odds ratio**	**95% CI**
User[b]	83	36	0.60	(0.39, 0.92)	49	34	0.85	(0.53, 1.36)
Pills per week								
≤7	65	24	0.50	(0.30, 0.83)	38	24	0.80	(0.47, 1.38)
>7	17	12	1.00	(0.46, 2.19)	11	8	0.79	(0.30, 2.07)
P-trend			.092				.38	
Duration of use, years								
<5	60	26	0.56	(0.34, 0.93)	35	21	0.64	(0.36, 1.13)
5–9	12	8	1.07	(0.42, 2.75)	7	7	1.72	(0.58, 5.15)
10 or more	11	2	0.31	(0.07, 1.43)	7	6	1.40	(0.43, 4.52)
P-trend			.036				.91	
Pill-years								
≤2.0	36	19	0.69	(0.38, 1.27)	19	15	0.82	(0.40, 1.66)
2.1–5.0	28	5	0.24	(0.09, 0.65)	16	6	0.48	(0.18, 1.27)
>5.0	18	12	1.01	(0.47, 2.18)	14	11	1.18	(0.51, 2.73)
P-trend			.059				.54	

[a]Adjusted for age, sex, residence, education, year of first registration at Mayo, family history of lymphoma, BMI, smoking history, alcohol use, RA and osteoarthritis.

[b]A user is defined as someone who reported use as least once per week for at least one year.

TABLE 4

Association aspirin, other NSAIDs and statins use with risk of NHL subtypes, Mayo Clinic Case-Control Study, 2002–2012[a]

	CLL/SLL			DLBCL			Follicular			Marginal zone			All other			
Regular use of agent	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**(*P*-heterogeneity**
Regular or extra strength aspirin																
Nonuser	398	1.00	Reference	280	1.00	Reference	335	1.00	Reference	114	1.00	Reference	271	1.00	Reference	
User[b]	87	1.11	(0.83, 1.47)	41	0.71	(0.48, 1.05)	70	1.03	(0.76, 1.40)	17	0.83	(0.48, 1.44)	64	1.17	(0.84, 1.62)	.24
Low dose aspirin																
Any use																
Nonuser	332	1.00	Reference	227	1.00	Reference	290	1.00	Reference	94	1.00	Reference	244	1.00	Reference	
User[b]	151	0.95	(0.75, 1.20)	88	0.74	(0.55, 1.00)	113	0.79	(0.61, 1.03)	37	0.80	(0.52, 1.22)	83	0.74	(0.55, 0.99)	.56
Duration of use, years																
<5	57	1.25	(0.89, 1.77)	20	0.56	(0.32, 0.97)	32	0.77	(0.50, 1.18)	6	0.52	(0.22, 1.23)	23	0.67	(0.40, 1.11)	
5–9	42	0.85	(0.58, 1.26)	32	1.04	(0.68, 1.59)	36	0.82	(0.55, 1.24)	15	1.10	(0.60, 2.03)	32	0.98	(0.64, 1.51)	
10+	52	0.80	(0.57, 1.13)	36	0.65	(0.42, 1.02)	45	0.79	(0.55, 1.14)	16	0.76	(0.41, 1.43)	28	0.61	(0.39, 0.95)	.24
P-trend		.22			.087			.12			.47			.043		
Ibuprofen																
Nonuser	382	1.00	Reference	268	1.00	Reference	318	1.00	Reference	108	1.00	Reference	274	1.00	Reference	
User[b]	104	1.30	(0.99, 1.69)	51	0.84	(0.58, 1.20)	85	1.28	(0.96, 1.70)	21	0.93	(0.55, 1.57)	56	0.98	(0.70, 1.38)	.15
Other anti-inflammatory NSAIDs																
Nonuser	450	1.00	Reference	301	1.00	Reference	380	1.00	Reference	121	1.00	Reference	320	1.00	Reference	
User[b]	35	1.02	(0.68, 1.53)	13	0.54	(0.28, 1.02)	23	0.75	(0.46, 1.22)	9	0.99	(0.47, 2.10)	14	0.63	(0.35, 1.12)	.33
COX-2 inhibitor																
Nonuser	460	1.00	Reference	296	1.00	Reference	385	1.00	Reference	125	1.00	Reference	320	1.00	Reference	
User[b]	24	0.65	(0.39, 1.07)	19	0.89	(0.52, 1.55)	18	0.60	(0.35, 1.05)	7	0.78	(0.33, 1.82)	15	0.72	(0.40, 1.28)	.84
Statins																
Never	317	1.00	Reference	223	1.00	Reference	274	1.00	Reference	93	1.00	Reference	229	1.00	Reference	
Ever	173	1.14	(0.91, 1.44)	94	0.86	(0.64, 1.14)	130	0.96	(0.75, 1.23)	41	0.86	(0.57, 1.32)	107	0.98	(0.75, 1.30)	.46

	CLL/SLL			DLBCL			Follicular			Marginal zone			All other			
Regular use of agent	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**N**	**OR**	**95% CI**	**(*P*-heterogeneity**
Other cholesterol drugs																
Never	448	1.00	Reference	294	1.00	Reference	371	1.00	Reference	124	1.00	Reference	312	1.00	Reference	
Ever	37	1.13	(0.74, 1.74)	20	0.95	(0.55, 1.65)	22	0.86	(0.52, 1.42)	9	1.12	(0.53, 2.38)	18	0.82	(0.47, 1.45)	.83

[a] Adjusted for age, sex, residence, education, year of first registration at Mayo, family history of lymphoma, BMI, smoking history, alcohol use, RA and osteoarthritis.

[b] A user is defined as someone who reported use as least once per week for at least one year.

TABLE 5

Association of statin, other cholesterol drug use and combination aspirin and statin use with NHL risk, Mayo Clinic Case-Control Study, 2002–2012

			Basic model[a]		Basic + SES[b]		Basic + confounders[c]	
Variable	**Controls**	**Cases**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Never user	1410	1136	1.00	Reference	1.00	Reference	1.00	Reference
Ever user	776	545	0.95	(0.83, 1.09)	0.93	(0.80, 1.08)	0.99	(0.85, 1.16)
Duration of use, years								
<5	239	168	0.91	(0.73, 1.14)	0.88	(0.70, 1.12)	0.91	(0.71, 1.16)
5–9	218	153	0.94	(0.75, 1.18)	0.94	(0.74, 1.21)	0.98	(0.76, 1.27)
10 or more	257	166	0.90	(0.72, 1.12)	0.89	(0.71, 1.12)	0.98	(0.77, 1.25)
P-trend			.27		.26		.76	
Other cholesterol drugs								
Never use	1987	1549	1.00	Reference	1.00	Reference	1.00	Reference
Ever use	159	106	0.92	(0.71, 1.20)	0.80	(0.60, 1.06)	0.97	(0.72, 1.31)
Duration of use, years								
<5	59	44	0.94	(0.62, 1.42)	0.92	(0.60, 1.42)	0.96	(0.61, 1.51)
5–9	33	22	0.95	(0.54, 1.68)	0.77	(0.42, 1.40)	1.22	(0.64, 2.32)
10 or more	43	27	0.93	(0.56, 1.55)	0.72	(0.41, 1.25)	0.81	(0.44, 1.50)
P-trend			.70		.14		.76	
Joint use of low dose aspirin[d] and statin								
Neither	1028	899	1.00	Reference	1.00	Reference	1.00	Reference
Aspirin only	365	216	0.67	(0.55, 0.82)	0.66	(0.53, 0.81)	0.73	(0.59, 0.91)
Both aspirin and statin	388	254	0.79	(0.65, 0.95)	0.77	(0.63, 0.94)	0.88	(0.71, 1.09)
Statin only	374	278	0.96	(0.80, 1.16)	0.93	(0.76, 1.14)	0.96	(0.78, 1.18)
Joint use of regular or extra strength aspirin[d] and statin								
Neither	1207	975	1.00	Reference	1.00	Reference	1.00	Reference
Aspirin only	183	147	0.92	(0.72, 1.17)	0.93	(0.72, 1.20)	1.00	(0.77, 1.30)
Both aspirin and statin	159	131	1.05	(0.81, 1.36)	1.02	(0.78, 1.34)	1.03	(0.78, 1.37)
Statin only	596	408	0.92	(0.79, 1.08)	0.90	(0.76, 1.07)	0.99	(0.83, 1.18)

[a]Adjusted for age, sex and residence.

[b] Further adjusted for education and year of first registration at Mayo.

[c] Further adjusted for education, family history of lymphoma, BMI, smoking history, alcohol use, RA and osteoarthritis.

[d] A user is defined as someone who reported use as least once per week for at least one year.