Research Article

Cancer Epidemiology, Biomarkers & Prevention

Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs and Risk of Non-Hodgkin Lymphoma

Lauren R. Teras, Susan M. Gapstur, Alpa V. Patel, Michael J. Thun, W. Ryan Diver, Yusheng Zhai, and Eric J. Jacobs

Abstract

Few large prospective studies have examined associations between nonsteroidal anti-inflammatory drug (NSAID) use and non-Hodgkin lymphoma (NHL). We examined the association between NSAID use and NHL incidence among 149,570 participants in the Cancer Prevention Study-II Nutrition cohort. Aspirin and nonaspirin NSAID use were reported at enrollment in 1992 and updated on periodic follow-up questionnaires. During follow-up through 2007, 1,709 incident NHLs were identified. Time-dependent hazard ratios were calculated using extended Cox regression. Compared to no use, current use of 60+ NSAID pills/month (aspirin and nonaspirin NSAIDs combined) was associated with slightly higher NHL incidence (hazard ratio [HR] = 1.26, 95% confidence interval [CI], 1.04–1.53), but no association with frequency of use was observed when NSAID exposure was lagged by approximately 2 years (HR = 1.08, 95% CI, 0.88–1.32). Long duration regular use (current use of 30+ pills/month for ≥5 years) was not associated with NHL incidence (HR = 1.09, 95% CI, 0.91–1.33). In subtype analyses, current use of 60+ NSAID pills/month was associated with follicular lymphoma incidence (HR = 1.87, 95% CI, 1.08–3.24). This association persisted when NSAID exposure was lagged (HR = 1.76, 95% CI, 1.04–2.98) and was similar for aspirin and nonaspirin NSAIDs. The association of current, but not lagged, NSAID use with risk of all NHL could be attributable to use of NSAIDs to relieve symptoms of undiagnosed NHL. However, the association with follicular lymphoma persisted in analyses where NSAID use was lagged and should be investigated further. These findings are particularly important for aspirin as the risks and benefits of prophylactic daily use are weighed. *Cancer Epidemiol Biomarkers Prev; 22(3); 422–8. ©2013 AACR.*

Introduction

There is accumulating evidence that aspirin reduces the incidence and mortality of several cancers (1, 2), beyond its established preventive effect on colorectal cancer (3). However, results of epidemiologic studies of nonsteroidal anti-inflammatory drugs (NSAIDs) in relation to non-Hodgkin lymphoma (NHL) are inconsistent. Positive, negative, and null associations have been reported, with some studies reporting an association with all NSAIDs, whereas others with just aspirin or nonaspirin NSAIDs (4–20). Most studies had limited statistical power, particularly for detailed analyses by frequency, duration, and type of NSAID use, and/or NHL subtype. Most previous studies were case control (13) and only 3 prospective studies had more than 135 cases (7, 19, 20), including one which examined only selective COX-2 inhibitors (7), and one which examined only aspirin (19). Summary measures from meta-analyses have been null (12–14), but, again, were based primarily on results from case-control studies, and were therefore subject to potential recall and selection bias. In addition, the meta-analyses were limited by the need to summarize across studies with widely varying definitions of NSAID use.

In this study, we examine the associations of 2 measures of NSAID use (frequency of current use, and long duration, regular use) with NHL incidence in the Cancer Prevention Study-II (CPS-II) Nutrition Cohort. This cohort is well suited to examine these associations because of its size, the availability of detailed, regularly updated information on aspirin and nonaspirin NSAID use, and the availability of NHL subtypes.

Materials and Methods

Study population

The CPS-II Nutrition Cohort (n = 184,188) is a prospective study conducted in 21 U.S. states and described in detail elsewhere (21). A mailed questionnaire in 1992/1993 collected sociodemographic, lifestyle, and medical history information. Biennial follow-up surveys beginning in 1997 collected updated exposure

Authors' Affiliation: Epidemiology Research Program, American Cancer Society, Atlanta, Georgia

Corresponding Author: Lauren R. Teras, Epidemiology Research Program, American Cancer Society, 250 Williams Street NW, Atlanta, GA 30303. Phone: 404-329-5785; Fax: 404-327-6450; E-mail: lauren.teras@cancer.org

doi: 10.1158/1055-9965.EPI-12-1158

information and ascertained new cancer diagnoses. Participants were excluded from this analysis for nonresponse to follow-up surveys ($n = 6,276$), previous cancer diagnoses ($n = 21,083$), unknown NSAID information at enrollment ($n = 7,134$), and unverified hematopoietic cancer reports on the first follow-up survey ($n = 125$). Among the 149,570 participants in the analytic cohort, 1,709 incident NHLs were identified during follow-up. The majority of these cancers were self-reported and then verified by medical record ($n = 989$) or state cancer registry linkage ($n = 333$). An additional 186 NHL cases were identified through linkage with the National Death Index and 133 were subsequently verified (22). Finally, 201 cases were identified through the process of verifying another cancer reported by the participant. NHL subtypes (diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and multiple myeloma) were defined using guidelines published by the International Lymphoma Epidemiology Consortium Pathology Working Group (23).

NSAID use

Information on use of aspirin and other NSAIDs was reported on mailed questionnaires in 1992/1993, 1997, 1999, 2001, 2003, and 2005. Historical information on use of aspirin (but not other NSAIDs) was also reported in 1982, when subjects were enrolled into the parent mortality cohort (24). The 1982 questionnaire asked about "times/month" of aspirin use. The 1992 and later questionnaires asked separately about aspirin and other NSAIDs. For each type, participants were asked about average days/month used, average number of pills taken on days used, and number of years used. We calculated a time-dependent variable for frequency in pills/month by multiplying days used per month by pills/day for each type of NSAID. For the primary analysis we considered a pill of low-dose aspirin the same as a pill of regular aspirin, but in a sensitivity analysis each low-dose aspirin pill (typically 81 mg) was counted as 1 quarter of a regular-dose aspirin pill (typically 325 mg). Participants who reported days/month they used a particular NSAID but did not report pills/day were assigned a value of 1 pill/day. The current number of pills/month of NSAIDs in each follow-up interval was categorized as 1 to <15, 15 to <30, 30 to <60, and 60+ pills/month and was updated at the time of each follow-up questionnaire (in 1997, 1999, 2001, 2003, 2005). In addition, because NSAID use for subclinical symptoms of NHL is of particular concern and the induction/latency period is unknown, we also calculated a lagged frequency variable defined by use reported on the next-to-most-recent questionnaire, rather than the most recent questionnaire. For example, use reported in 1992 was used to predict risk during the interval between the 1997 and 1999 questionnaires and use reported in 1997 was used to predict risk during the 1999–2001 interval. The first interval (1992–1997) was lagged by excluding the first 2 years of follow-up.

Analyses of duration of regular (≥30 NSAID pills/month) use of NSAIDs used the following categories: (a) never reported use (never users), (b) past or less than regular NSAID use only, (c) current regular NSAID use of <5 years, and (d) current regular NSAID use of ≥5 years. During the 1992–1997 follow-up interval, participants were categorized as having ≥5 years of regular NSAID use if they reported at least 5 years of use on their 1992 questionnaire and also reported regular NSAID use on both the 1982 and 1992 questionnaires. During the 1997 to 1999 follow-up interval, participants were categorized as having ≥5 years of regular NSAID use if they reported regular NSAID use on both the 1992 and 1997 questionnaires. During later follow-up intervals, participants were categorized as having ≥5 years of regular NSAID use if they reported regular NSAID use on the 3 most recent questionnaires (e.g. on the 1992, 1997, and 1999 questionnaires for the 1999–2001 interval). In each follow-up interval, participants who had not reported NSAID use on any previous questionnaire were categorized as never users, whereas participants who were neither never users nor current regular users were categorized as "past or less than regular use only."

Both frequency and duration of regular NSAID use were calculated by summing pills per month for each type of NSAID to create a total NSAID variable. In addition, we also examined aspirin and nonaspirin NSAID use separately. Based on results from other studies, we could not rule out different associations of these 2 NSAID types with NHL risk. To ensure we were studying the association of current use of each type of NSAID without the influence of the other, participants were classified into mutually exclusive categories: never NSAID use, former NSAID use, current aspirin-only, current nonaspirin NSAIDs only.

Statistical analyses

Person-time was calculated as days between enrollment date and cancer diagnosis date, death date, date of last returned survey, or end of follow-up (June 30, 2007). Participants with missing NSAID information on a follow-up survey were censored during the subsequent follow-up interval but were reentered into the analysis if valid NSAID information was reported on the next survey. However, participants were permanently censored if NSAID information was missing on 2 consecutive surveys. In analyses of specific NSAID types (aspirin/nonaspirin), participants were censored on the date they reported use of the other type of NSAID. In addition, participants who self-reported a hematopoietic cancer that could not be verified were censored on the date of their last cancer-free questionnaire.

Extended Cox regression (25) was used to calculate time-dependent hazard ratios (HR) and 95% confidence intervals (CI) for the associations between NSAID use and

NHL incidence overall, DLBCL, follicular lymphoma, CLL/SLL, and multiple myeloma. All models were stratified on enrollment age and used follow-up time as the time scale. Multivariable models included sex, family history of hematopoietic cancers, race, alcohol intake, education, smoking status, body mass index (BMI), sitting time, diabetes status, rheumatoid arthritis status (starting in 2001), cholesterol-lowering drug use, acetaminophen use, and postmenopausal hormone use.

Results

On average, participants were aged 63 years at the start of follow-up and most identified as white (97%). In 1992, 43% of the participants reported never use of NSAIDs and 31% were regular users. Those who reported regular NSAID use in 1992/1993 were more likely to be slightly older, have a BMI $\geq$ 30 kg/m^2, be former smokers, drink at least 2 drinks daily, currently use cholesterol-lowering drugs, and to report diabetes than participants who never or only occasionally used NSAIDs (Table 1). And in 2001, regular NSAID users were more likely to report rheumatoid arthritis than other participants.

Total NSAID use was not associated with NHL risk when defined as frequency of current use or duration of regular use (Table 2). The hazard ratio (HR) for participants who reported currently taking $\geq$60 pills/month compared to never users was statistically significant (HR = 1.26, 95% CI, 1.04–1.53) but was attenuated (HR = 1.08, 95% CI, 0.88–1.32) in the lagged model (Table 2). For NHL subtypes, 60+ pills/month of any NSAID use compared to never use was associated with a higher risk of follicular lymphoma (HR = 1.87, 95% CI, 1.08–3.24). This association remained when the lagged NSAID variable was used (HR = 1.76, 95% CI, 1.04–2.98). The hazard ratio for 30-<60 pills/month was elevated but not statistically significant, and there was no association with any other frequency of use. The elevated risk of follicular lymphoma was strongest for long-term (5+ years), regular NSAID users.

Table 1. Non-Hodgkin lymphoid neoplasm risk factors by NSAID use at enrollment of the CPS-II Nutrition Cohort in 1992–1993

	No current NSAID use (n = 64,755)	Less than daily NSAID use (1–29 pills/month) (n = 37,702)	Daily NSAID use (30+ pills/month) (n = 47,113)
Age at baseline (years)			
<60	31.5%	36.0%	27.2%
60 to <70	53.3%	51.3%	54.4%
70 to <80	14.9%	12.4%	17.9%
80+	0.3%	0.3%	0.4%
Women	54.6%	54.0%	48.2%
White race	96.8%	97.4%	98.1%
Education			
High school or less	32.9%	30.6%	31.5%
Some college	27.8%	29.0%	29.6%
College graduate	38.6%	39.8%	38.2%
Unknown	0.7%	0.6%	0.6%
Family history of hematopoietic cancer	3.4%	3.5%	3.5%
Body mass index (kg/m^2)			
<25.0	48.0%	45.1%	39.1%
25.0 to <30.0	37.7%	39.6%	41.7%
≥30.0	12.9%	13.9%	17.7%
Smoking status			
Never	46.6%	44.5%	39.7%
Former	43.2%	45.3%	50.7%
Current	8.9%	8.8%	8.6%
Alcohol use			
Nondrinker	41.5%	36.3%	39.9%
<1 drink/day	36.7%	40.7%	36.9%
1–2 drinks/day	10.0%	11.5%	11.1%
>2 drinks/day	8.3%	8.6%	9.8%
Current use of cholesterol-lowering drugs	6.7%	7.0%	13.4%
Diabetes in 1992	6.6%	6.0%	9.1%

Table 2. Risk of non-Hodgkin lymphoma by frequency of current NSAID use and duration of regular[a] NSAID use, CPS-II Nutrition Cohort, 1992–2007

		All NHL		DLBCL		Follicular		CLL/SLL		Multiple Myeloma	
	Person Years	NHL Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)
Current NSAID pills/month											
No reported NSAID use	201,712	199	1.00–	39	1.00–	21	1.00–	53	1.00–	36	1.00–
Former NSAID use	366,405	404	1.08 (0.91–1.28)	79	1.01 (0.68–1.49)	43	1.08 (0.64–1.82)	97	1.00 (0.71–1.40)	76	1.15 (0.77–1.72)
1-<15	221,206	222	1.05 (0.86–1.27)	42	0.96 (0.62–1.49)	32	1.44 (0.82–2.51)	53	0.96 (0.65–1.41)	44	1.20 (0.77–1.87)
15-<30	135,316	129	0.96 (0.77–1.20)	25	0.93 (0.56–1.54)	25	1.76 (0.98–3.16)	29	0.80 (0.51–1.27)	21	0.89 (0.52–1.53)
30-<60	409,505	518	1.07 (0.91–1.27)	117	1.15 (0.79–1.68)	69	1.45 (0.88–2.40)	129	1.01 (0.73–1.41)	87	1.00 (0.67–1.49)
60+	181,269	237	1.26 (1.04–1.53)	42	1.08 (0.69–1.69)	36	1.87 (1.08–3.24)	55	1.11 (0.75–1.63)	46	1.40 (0.89–2.18)
Lagged[c] NSAID pills/month											
No reported NSAID use	237,288	198	1.00–	38	1.00–	24	1.00–	55	1.00–	36	1.00–
Former NSAID use	385,051	402	1.18 (1.00–1.41)	86	1.25 (0.85–1.84)	48	1.17 (0.71–1.91)	85	0.91 (0.65–1.29)	76	1.24 (0.83–1.85)
1-<15	238,151	208	1.04 (0.85–1.26)	40	1.00 (0.64–1.56)	23	0.94 (0.52–1.67)	57	1.03 (0.71–1.50)	38	1.09 (0.69–1.73)
15-<30	147,610	124	0.96 (0.77–1.20)	26	1.01 (0.61–1.67)	15	0.97 (0.51–1.85)	31	0.85 (0.55–1.33)	16	0.70 (0.39–1.26)
30-<60	384,013	447	1.10 (0.92–1.31)	96	1.18 (0.80–1.73)	62	1.32 (0.81–2.15)	115	1.03 (0.74–1.44)	73	0.95 (0.63–1.44)
60+	187,239	185	1.08 (0.88–1.32)	36	1.05 (0.66–1.67)	36	1.76 (1.04–2.98)	38	0.81 (0.53–1.24)	38	1.23 (0.77–1.95)
Duration of regular[a] NSAID use											
No reported NSAID use	201,712	199	1.00–	39	1.00–	21	1.00–	53	1.00–	36	1.00–
Former or less than regular NSAID use	722,928	755	1.05 (0.89–1.23)	146	0.98 (0.69–1.41)	100	1.32 (0.82–2.12)	179	0.94 (0.69–1.29)	141	1.13 (0.78–1.63)
Current regular NSAID use <5 years	391,742	473	1.14 (0.96–1.35)	99	1.15 (0.79–1.68)	61	1.49 (0.90–2.47)	122	1.09 (0.79–1.52)	77	1.04 (0.70–1.56)
Current regular NSAID use 5+ years	199,031	282	1.10 (0.91–1.33)	60	1.07 (0.70–1.63)	44	1.78 (1.03–3.09)	62	0.92 (0.62–1.36)	56	1.24 (0.79–1.94)

[a]Regular use defined as 30+ pills per month.

[b]Multivariable models adjusted for sex, family history of hematopoietic cancers, race, alcohol intake, education, smoking status, BMI, sitting time, diabetes status, rheumatoid arthritis status (starting in 2001), cholesterol-lowering drug use, acetaminophen use, and postmenopausal hormone use.

[c]Lagged analysis used NSAID information from the previous survey (e.g. for the 1999–2001 interval NSAID information is from 1997).

Table 3. Risk of non-Hodgkin lymphoma by frequency of current aspirin and nonaspirin NSAID use and duration of regular[a] aspirin and nonaspirin NSAID use, CPS-II Nutrition Cohort, 1992–2007

			All NHL		DLBCL		Follicular		CLL/SLL		Multiple Myeloma	
		Person Years	NHL Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)	Cases	HR[b] (95%CI)
Current NSAID pills/month												
No reported NSAID use		201,712	199	1.00 –	39	1.00 –	21	1.00 –	53	1.00 –	36	1.00 –
Former NSAID use only		329,902	359	1.09 (0.92–1.30)	67	0.99 (0.66–1.47)	40	1.16 (0.68–1.98)	85	1.00 (0.71–1.42)	70	1.19 (0.79–1.79)
Aspirin[†]	1-<15	101,895	116	1.20 (0.95–1.51)	24	1.27 (0.76–2.11)	13	1.29 (0.65–2.59)	32	1.24 (0.80–1.93)	23	1.31 (0.77–2.22)
	15-<30	69,507	63	0.89 (0.67–1.18)	9	0.65 (0.32–1.35)	12	1.65 (0.81–3.36)	16	0.83 (0.47–1.45)	12	0.94 (0.49–1.81)
	30-<60	224,435	286	1.04 (0.86–1.25)	68	1.16 (0.77–1.75)	30	1.06 (0.59–1.89)	72	1.00 (0.69–1.44)	49	0.99 (0.64–1.55)
	60+	39,909	56	1.42 (1.06–1.92)	10	1.28 (0.64–2.58)	12	3.09 (1.51–6.32)	10	0.95 (0.48–1.87)	14	1.97 (1.06–3.67)
Nonaspirin[†]	1-<15	55,167	41	0.85 (0.61–1.20)	9	0.94 (0.45–1.95)	5	0.98 (0.37–2.63)	11	0.87 (0.45–1.67)	8	0.96 (0.44–2.07)
	15-<30	17,828	17	1.18 (0.72–1.94)	4	1.43 (0.51–4.04)	5	3.09 (1.14–8.37)	3	0.82 (0.25–2.62)	1	0.39 (0.05–2.87)
	30-<60	26,687	31	1.34 (0.92–1.97)	7	1.52 (0.68–3.42)	7	3.08 (1.30–7.30)	5	0.83 (0.33–2.08)	4	0.94 (0.33–2.64)
	60+	34,976	42	1.36 (0.97–1.91)	7	1.09 (0.48–2.45)	8	2.71 (1.19–6.18)	8	1.01 (0.48–2.13)	9	1.58 (0.76–3.31)
Lagged[c] NSAID pills/month												
No reported NSAID use		225,489	201	1.00 –	40	1.00 –	24	1.00 –	55	1.00 –	36	1.00 –
Former NSAID use only		330,497	372	1.21 (1.02–1.44)	80	1.24 (0.84–1.82)	47	1.31 (0.80–2.15)	76	0.92 (0.65–1.31)	70	1.25 (0.83–1.88)
Aspirin[†]	1 to <15	105,844	111	1.22 (0.97–1.54)	21	1.15 (0.68–1.96)	10	0.94 (0.45–1.98)	33	1.32 (0.85–2.03)	24	1.49 (0.89–2.51)
	15 to <30	72,308	68	1.03 (0.78–1.35)	13	0.96 (0.51–1.81)	5	0.67 (0.25–1.76)	14	0.76 (0.42–1.37)	14	1.18 (0.64–2.20)
	30 to <60	195,470	259	1.14 (0.94–1.38)	57	1.19 (0.78–1.81)	29	1.09 (0.63–1.92)	70	1.16 (0.80–1.67)	44	1.06 (0.67–1.67)
	60+	41,639	41	1.15 (0.82–1.62)	8	1.14 (0.53–2.44)	10	2.53 (1.21–5.32)	5	0.51 (0.21–1.28)	10	1.56 (0.77–3.16)
Nonaspirin[†]	1 to <15	51,853	37	0.89 (0.63–1.27)	6	0.71 (0.30–1.68)	7	1.40 (0.60–3.28)	11	0.98 (0.51–1.88)	3	0.41 (0.13–1.33)
	15 to <30	17,365	18	1.41 (0.87–2.30)	5	1.91 (0.75–4.86)	2	1.30 (0.30–5.56)	4	1.15 (0.42–3.19)	1	0.45 (0.06–3.28)
	30 to <60	26,322	31	1.55 (1.06–2.27)	7	1.70 (0.76–3.82)	5	2.26 (0.85–5.98)	7	1.30 (0.59–2.86)	2	0.53 (0.13–2.23)
	60+	34,989	42	1.54 (1.10–2.16)	6	1.05 (0.44–2.49)	10	3.37 (1.59–7.14)	8	1.10 (0.52–2.32)	7	1.40 (0.61–3.17)
Duration of current, regular[a] NSAID use												
No reported NSAID use		201,712	199	1.00 -	39	1.00 –	21	1.00 –	53	1.00 –	36	1.00 –
Former or less than regular NSAID use		574,354	596	1.07 (0.91–1.26)	113	1.00 (0.69–1.45)	75	1.27 (0.78–2.08)	147	1.00 (0.73–1.37)	114	1.15 (0.79–1.68)
Current, regular Aspirin use	<5 years	140,271	172	1.04 (0.84–1.28)	41	1.16 (0.74–1.82)	19	1.15 (0.61–2.17)	38	0.87 (0.57–1.33)	35	1.19 (0.74–1.92)
	5+ years	124,073	170	1.15 (0.93–1.41)	37	1.20 (0.76–1.92)	23	1.54 (0.84–2.85)	44	1.13 (0.75–1.71)	28	1.04 (0.63–1.74)
Current, regular Nonaspirin use[‡]	<5 years	15,662	19	1.07 (0.66–1.73)	4	1.00 (0.35–2.83)	4	2.23 (0.75–6.63)	5	1.10 (0.43–2.79)	2	0.65 (0.15–2.71)
	5+ years	7,090	12	1.55 (0.86–2.79)	4	2.23 (0.78–6.35)	2	2.66 (0.61–11.6)	1	0.51 (0.07–3.73)	2	1.48 (0.35–6.25)

[a]Regular use defined as 30+ pills per month.

[b]Multivariable models adjusted for sex, family history of hematopoietic cancers, race, alcohol intake, education, smoking status, BMI, sitting time, diabetes status, rheumatoid arthritis status (starting in 2001), cholesterol-lowering drug use, acetaminophen use, and postmenopausal hormone use.

[c]Lagged analysis used NSAID information from the previous survey (e.g. for the 1999–2001 interval NSAID information is from 1997).

[†]Aspirin and nonaspirin categories are mutually exclusive. Aspirin users never reported use of used nonaspirin NSAIDs and vice versa.

‡Includes only follow-up from 1997 to 2007 because duration of use of this NSAID could not be estimated until 1997.

In analyses by NSAID type (Table 3), use of 60+ pills/month of aspirin-only or nonaspirin-NSAIDs-only, was associated with increased NHL risk. However, the association with aspirin was attenuated when the lagged variable was used, whereas the association with nonaspirin strengthened slightly. Both aspirin and nonaspirin NSAID use were associated with a statistically significant 2- to 3-fold higher risk of follicular lymphoma which remained when the lagged variables were used. Results were not meaningfully changed in sensitivity analyses counting low-dose aspirin as one-fourth of a regular aspirin (data not shown).

Discussion

Results from this prospective study do not support a strong association between NSAID use and overall NHL incidence. A statistically significant positive association was observed between current use of 60+ pills/month of NSAIDs and NHL risk. However, this association was no longer apparent when NSAID exposure was lagged, suggesting that the association with current NSAID use might be attributed to NSAID use for symptoms of undiagnosed NHL.

These results for all NSAIDs extend our previous null findings for long-term regular aspirin use and NHL overall (not including multiple myeloma or CLL; ref. 19) and are consistent with 3 meta-analyses that found no relationship between NHL incidence and ever/never or a heterogeneous "maximum exposure" to aspirin (12, 14) or between all NSAIDs and all hematopoietic malignancies (13). In the Vitamins and Lifestyle cohort (20), the largest ($n = 577$ cases) study to examine associations with aspirin and other NSAIDs, no associations of aspirin or other NSAID use with risk of hematologic malignancies, NHL, or NHL subtypes were found. However, NSAID use was not updated throughout follow-up in that study and the resulting potential misclassification is unknown. Among 2 earlier cohort studies, one reported a nonsignificant reduced risk of lymphoma with aspirin used 1 month before interview ($n = 94$ cases; ref. 18), and the other a statistically significant higher risk of NHL with aspirin and other NSAIDs, but no dose response was observed ($n = 131$ cases; ref. 5). In general, previous cohort studies reported positive (4, 5, 7) or null (19, 20) associations between NSAID use and NHL whereas most case-control studies reported inverse (8–11, 15), associations. Potential recall bias in the case-controls studies may have influenced the study results and contributed to these inconsistent findings.In analyses by NHL subtype, we observed an association between current use of 60+ pills/month of NSAIDs use and increased risk of follicular lymphoma that persisted when NSAID exposure was lagged and was strongest for long-term, regular NSAID users. Few other studies examined NSAID use and NHL subtypes. One case-control study reported a positive association between long-term, regular NSAID use and DLBCL only (17), whereas another reported a lower risk of several NHL subtypes with 4 or more consecutive weeks of NSAID use (8).

Our study has some important strengths, including its size and the availability of prospectively collected, regularly updated NSAID use data. With over 1,700 cases this is one of the largest studies to date on this topic. Second, the availability of regularly updated information on type and frequency of NSAID use allowed us to examine mutually exclusive groups of never users, current aspirin-only users, and current nonaspirin only users. In addition, it allowed us to examine a highly exposed group of NSAID users (regular users of 5+ years). This is one of the first studies to comprehensively examine NSAID use and the most common NHL subtypes, but sample sizes for these analyses were still modest and results require replication. In addition, the impact of unknown confounders (e.g., autoimmune conditions other than rheumatoid arthritis) on our results is unknown.

In summary, results of this study support an association between regular NSAID use and follicular lymphoma incidence but no other NHL subtype. This association with follicular lymphoma should be further investigated in large (or consortial) studies. This is particularly important for aspirin as the risks and benefits of prophylactic, daily use are weighed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: L.R. Teras, S.M. Gapstur, A.V. Patel
Development of methodology: L.R. Teras, E.J. Jacobs
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): S.M. Gapstur, A.V. Patel
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L.R. Teras, W.R. Diver, Y. Zhai, E.J. Jacobs
Writing, review, and/or revision of the manuscript: L.R. Teras, S.M. Gapstur, A.V. Patel, W.R. Diver, E.J. Jacobs
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.R. Teras
Study supervision: S.M. Gapstur

Grant Support

The American Cancer Society (ACS) has funded the creation, maintenance, and follow-up of the Cancer Prevention Study II Nutrition cohort. All of the authors were employed by the Society during the course of this analysis.

Received October 11, 2012; revised December 27, 2012; accepted January 3, 2013; published OnlineFirst January 17, 2013.

References

1. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011;377:31–41.

2. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 2012;379:1602–12.
3. Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. Nat Rev Clin Oncol 2012;9:259–67.
4. Bernstein L, Ross RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. Cancer Res 1992;52: 5510s–5s.
5. Cerhan JR, Anderson KE, Janney CA, Vachon CM, Witzig TE, Habermann TM. Association of aspirin and other non-steroidal anti-inflammatory drug use with incidence of non-Hodgkin lymphoma. Int J Cancer 2003;106:784–8.
6. Kato I, Koenig KL, Shore RE, Baptiste MS, Lillquist PP, Frizzera G, et al. Use of anti-inflammatory and non-narcotic analgesic drugs and risk of non-Hodgkin's lymphoma (NHL) (United States). Cancer Causes Control 2002;13:965–74.
7. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to cyclooxygenase-2 inhibitors and risk of cancer: nested case-control studies. Br J Cancer 2011;105:452–9.
8. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol 2003;158:316–27.
9. Zhang Y, Holford TR, Leaderer B, Zahm SH, Boyle P, Morton LM, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control 2004;15:419–28.
10. Baker JA, Weiss JR, Czuczman MS, Menezes RJ, Ambrosone CB, Moysich KB. Regular use of aspirin or acetaminophen and risk of non-Hodgkin lymphoma. Cancer Causes Control 2005;16:301–8.
11. Hoeft B, Becker N, Deeg E, Beckmann L, Nieters A. Joint effect between regular use of non-steroidal anti-inflammatory drugs, variants in inflammatory genes and risk of lymphoma. Cancer Causes Control 2008;19:163–73.
12. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol 2012; 13:518–27.
13. Bernatsky S, Lee JL, Rahme E. Non-Hodgkin's lymphoma—meta-analyses of the effects of corticosteroids and non-steroidal anti-inflammatories. Rheumatology (Oxford) 2007;46:690–4.
14. Bosetti C, Gallus S, La Vecchia C. Aspirin and cancer risk: an updated quantitative review to 2005. Cancer Causes Control 2006; 17:871–88.
15. Beiderbeck AB, Holly EA, Sturkenboom MC, Coebergh JW, Stricker BH, Leufkens HG. Prescription medications associated with a decreased risk of non-Hodgkin's lymphoma. Am J Epidemiol 2003; 157:510–6.
16. Flick ED, Chan KA, Bracci PM, Holly EA. Use of nonsteroidal antiinflammatory drugs and non-Hodgkin lymphoma: a population-based case-control study. Am J Epidemiol 2006;164:497–504.
17. Chang ET, Smedby KE, Hjalgrim H, Schollkopf C, Porwit-MacDonald A, Sundstrom C, et al. Medication use and risk of non-Hodgkin's lymphoma. Am J Epidemiol 2005;162:965–74.
18. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5: 138–46.
19. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst 2007;99:608–15.
20. Walter RB, Milano F, Brasky TM, White E. Long-term use of acetaminophen, aspirin, and other nonsteroidal anti-inflammatory drugs and risk of hematologic malignancies: results from the prospective Vitamins and Lifestyle (VITAL) study. J Clin Oncol 2011;29:2424–31.
21. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, et al. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. Cancer 2002;94:2490–501.
22. Calle EE, Terrell DD. Utility of the National Death Index for ascertainment of mortality among cancer prevention study II participants. Am J Epidemiol 1993;137:235–41.
23. Turner JJ, Morton LM, Linet MS, Clarke CA, Kadin ME, Vajdic CM, et al. InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions. Blood 2010;116:e90–8.
24. Garfinkel L. Selection, follow-up, and analysis in the American Cancer Society prospective studies. Natl Cancer Inst Monogr 1985;67:49–52.
25. Therneau TM, Grambsch PM. Modeling survival data: extending the Cox model. New York: Springer; 2000.