Hematological Oncology
Hematol Oncol 2015; **33**: 176–186
Published online 23 October 2014 in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hon.2165

Original Research Article

Use of non-steroidal anti-inflammatory drugs and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis

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Received 15 May 2014
Revised 25 July 2014
Accepted 1 August 2014

Abstract

Epidemiological study findings regarding the association between use of non-steroidal anti-inflammatory drugs (NSAIDs) and risk of non-Hodgkin lymphoma (NHL) have been inconsistent. We aimed to systematically review epidemiological studies of the association and calculate pooled relative risks using meta-analytic methods. We searched eight electronic literature databases and three clinical trial registers to identify all studies (including observational studies and randomized clinical trials) of the association published prior to October 2013. Identified studies were independently reviewed by two researchers. We used a random effects model to calculate pooled odds ratio (PORs). Heterogeneity amongst studies was examined using Cochran's Q and I-squared (I^2) tests; and sources of heterogeneity were explored using subgroup and meta-regression analyses. A total of 17 studies (12 case-control studies and five cohort studies), all adult studies, were included. Use of NSAIDs was not associated with overall risk of NHL [POR = 1.05, and 95% confidence interval (95% CI) 0.90–1.22] or NHL subtypes including B-cell lymphoma, T-cell lymphoma, follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Aspirin use was associated with reduced risk of CLL/SLL (POR = 0.70, 95% CI 0.54–0.91) but not with the risk of all NHLs (POR = 1.02, 95% CI 0.89–1.17). Use of non-aspirin NSAIDs was associated with increased risk of NHL (POR = 1.41, 95% CI 1.01–1.97) amongst females only. The epidemiologic evidence remains inconclusive. Effects of NSAIDs may differ by drug type, NHL subtype, and sex and more studies taking into consideration these differences are needed.

Keywords: **non-Hodgkin lymphoma; risk factors; meta-analysis; non-steroidal anti-inflammatory drug; aspirin**

Introduction

Non-Hodgkin lymphomas (NHLs) as a group of lymphoproliferative disorders are amongst the seven most common cancers in the developed world [1], but the etiology of most NHLs remains unknown [2]. Acquired immunosuppression, autoimmune disorders (e.g. rheumatoid arthritis) and certain infectious agents (e.g. Epstein–Barr virus) were associated with increased risk of some NHL subtypes, but they collectively represent approximately 50% of all NHLs [2]. Use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, has been consistently associated with reduced risk of several solid cancers including colon and prostate cancers [3,4]. Inhibition of cyclooxygenase (COX) enzymes, which decreases the production of prostaglandins, appears to be the mechanism by which NSAIDs can prevent the development of these cancers [5]. Animal and laboratory studies indicate that NSAIDs induce apoptosis of hematological tumour cells via this mechanism [6]. However, epidemiological studies have thus far produced conflicting results, with some studies suggesting increased risk of NHLs amongst NSAIDs users [7–11] and others finding no association [12–17], or even a decreased risk [18–21]. Bernatsky and colleagues conducted a meta-analysis of studies published before 2007 and found that, overall, NSAID use was not associated with the risk of NHLs [22]. Their analysis, however, was limited by a lack of information on the

effects of NSAIDs on specific NHL histological subtypes. Since the publication of their findings, several reports [9,16,17,23,24], including three from large cohort studies [9,17,24], have been published. We sought to update the evidence on the association by including more recent studies and to further our understanding by stratifying the analysis by NHL and NSAID types. We conduct and report the review according to the recommendations by the Meta-analysis of Observational Studies in Epidemiology Group [25].

Methods

Literature search and study inclusion

We aimed to include both observational studies and randomized clinical trials that examined the association between NSAID use and NHL incidence or mortality, however our search did not identify any randomized clinical trials. Otherwise, we did not impose any exclusion criteria. Medications of interest were all types of NSAIDs, including both aspirin and non-aspirin NSAIDs (NA-NSAIDs). We searched eight bibliographic databases and three clinical trial registries (Supplemental Materials) using both Medical Subject Headings and free text words including the standard drug terminology used in the WHO Anatomical Therapeutic Chemical classification system [26]. In addition, references cited by identified articles were searched manually to identify additional reports that may have been missed by the electronic queries.

Relevance of articles was determined independently by two reviewers based on reviewing the titles and the abstracts, and full-text if necessary. We decided not to assess the quality of studies because the validity of quality scoring in meta-analyses of observational studies and clinical trials is controversial [27,28]. However, a form was developed to extract information on study quality domains (e.g. study design, selection bias, outcome and drug information sources and ascertainment methods, and confounders adjusted for) and other study characteristics (e.g. study population, NSAID type and NHL type), and analyses were stratified by these characteristics. Data extraction was performed independently by two reviewers and any differences were reconciled and adjudicated by a third reviewer if necessary.

Data analysis

Where available, adjusted relative risk (RR) measures (i.e. risk/rate ratios or odd ratios) were used in the analysis, otherwise crude measures were used. We used random effects models to estimate pooled odds ratios (PORs) [29]. We examined potential heterogeneity between studies using Cochran's Q and the I-squared (I^2) tests at a significance level of 0.05 [29]. $I^2 > 50\%$ was considered the presence of heterogeneity amongst studies [29]. We used Egger's test and Begg's test to assess funnel plot asymmetry related to reporting bias and small-study-effects [30,31].

We stratified our analyses by drug type (total NSAIDs, aspirin and NA-NSAIDs) and by NHL subtype [B-cell lymphoma, T-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, diffuse large B-cell lymphoma]. Whenever possible, we also stratified the analysis by sex. To assess potential sources of heterogeneity, we conducted subgroup analyses by grouping studies using other study characteristics including geographic region [United States (USA) vs others], study design (case-control vs cohort), source population (general population vs otherwise), method of case ascertainment (pathology review vs other) and information source (hospital records vs others), drug and confounder information source (administrative database vs others), study size as measured by the estimates' precision (RR upper/lower limits ratio ≥ 2 vs < 2), and whether adjustment for confounding by indication or by use of other medications was performed. Whenever possible, analyses were also stratified by duration of drug use ($\geq$6 months vs $<$6 months). We used meta-regression to further investigate the associations between these factors and pooled ORs (log scale) [32]. To assess excessively influential studies, we repeated the analysis after omitting a study at each run. In addition to the primary analyses, we conducted a series of sensitivity analyses by including studies of blood cancers or overall lymphoma, by excluding studies involving high-risk participants (e.g. AIDS patients and rheumatoid arthritis patients) and by excluding studies of selective COX-2 inhibitors. All analyses were undertaken using Stata 11.0 (Stata Corp, College Station, Texas, USA).

Results

A total of 23 articles met the inclusion criteria on the basis of abstract and title (Figure 1). Of these, three articles [33–35] reporting on studies of all blood cancers or all lymphomas were not included in primary analysis although the effect of their exclusion was explored in sensitivity analyses. Two articles [19,20] reported findings for total NHL and for subtypes separately using the same study cohort, and both were included in the subgroup analyses (but counted as one study). Two articles [36,37] that duplicated the analyses of another two articles [8,9] by the same research teams were excluded. As a result, there were 17 unique studies (12 case-control and five cohort studies) included in the primary meta-analysis (Table 1). Of them, the associations between risk of NHLs (overall and subtypes) and NSAID use (as a class) were examined in 13 studies; aspirin use in 11 studies and NA-NSAID use in eight studies.

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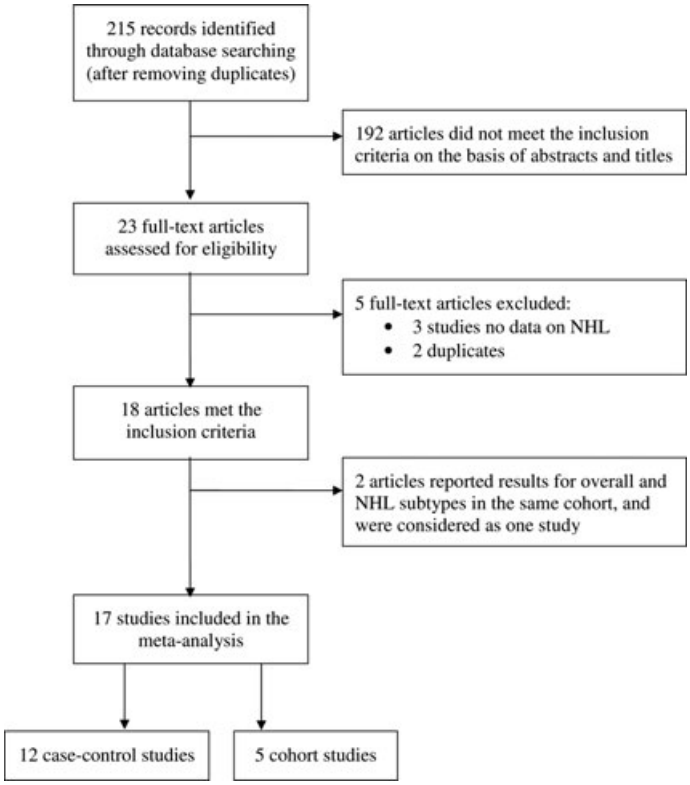

Figure 1. Flow diagram of study selection

The primary meta-analysis included a total of 12 942 NHL patients aged >16 years. All studies were undertaken in developed countries: 12 in USA and five in Europe. NHL cases were identified through cancer registries or hospital discharge records but one study has also identified 186 cases (of a total of 1709 cases) through a death registry [9]. Different approaches were used to measure NSAID use (administrative database, interview and self-completed questionnaire). Eight studies examined both total NHL and subtypes in relation to NSAID use. Most studies ($n = 13$) assessed the effects of overall use of NSAIDs as well as that of specific types (aspirin and NA-NSAIDs). Most studies used frequency and/or duration to define exposure to NSAID use, with only one study measuring dose of use [9]. There was little evidence for funnel plot asymmetry, and the Egger's and Begg's tests did not suggest reporting bias or small-study-effects.

Use of NSAIDs (measured as a class) was not associated with the risk of diagnosis with any NHL [pooled OR (POR) = 1.05, 95% CI 0.90–1.22] or the risk of diagnosis with several NHL subtypes (Figure 2). The studies of total NHL were diverse in terms of design and other characteristics (p for heterogeneity test = 0.001, $I^2 = 62.7\%$). In subgroup analyses of studies of NSAID use (as a class) and overall risk of NHLs, we observed some differences in PORs by study characteristics but none of them were statistically significant: studies largely or completely involving female participants, studies that did not take into account latent period, and studies with larger RR errors had slightly stronger positive associations; studies using hospital records as the source of cases and studies using administrative data as the source of drug use information tended to have relatively stronger inverse associations (see supplemental materials). In multivariate meta-regression analyses, larger RR errors was associated with greater POR. Influential analysis indicated that the POR was not significantly influenced by any single study. Sensitivity analyses supported the robustness of the POR estimation: excluding the study of high-risk participants (i.e. rheumatoid arthritis patients) [11], including the three studies of all blood cancers [34] or all lymphomas [33,35], including the four studies focusing aspirin use [14,21,24,38] and excluding the study of selective COX2 inhibitors [16] from the models produced almost identical PORs for total NHL and NSAID use.

Aspirin use was not associated with the risk of diagnosis with any NHL (POR = 1.02, 95% CI 0.89–1.17), and there was no heterogeneity (p for heterogeneity test = 0.175, $I^2 = 27.5\%$), as shown in Figure 3. Excluding the study of high-risk participants (i.e. rheumatoid arthritis and AIDS patients) [11,14] did not change POR appreciably. Subgroup analyses did not show any effect modifications by the study characteristics. There were no associations between aspirin use and any of NHL subtypes with one

DOI: 10.1002/hon

Table 1. Characteristics of studies included in the review

Study	Country	Study period	Source population	Case data source	NHL ascertainment	No. of cases	Age	Medications of interest	Medication usage information source	Definition of exposed subjects	Latent period considered?
Case-control studies											
Baecklund, 2006 (11)	Swedish	1964–1995	Rheumatoid arthritis patients	Hospital discharge records	NHL	378	≥16	Aspirin, Total NSAIDs	Hospital records	Duration (≥4 weeks)	No
Baker, 2005 (21)	USA	1982–1998	Hospital patients	Hospital discharge records	NHL, B-cell (and subtypes), T-cell	625	57 (mean)	Aspirin	Self-completed questionnaire	Frequency, duration, cumulative dose (tablets*years)	No
Beiderbeck, 2003 (15)	Netherlands	1991–1998	General population	Hospital discharge records	NHL	211	>20	Total NSAIDs	Pharmaceutical use database	Duration (≥2 years)	1, 3 and 5 years
Bernstein, 1992 (13)	USA	1979–1982	General population	Population cancer registry	NHL	619	19–75	Total NSAIDs	Interview	Duration (≥1 month)	No
Chang, 2005 (8)	Denmark and Sweden	1999–2002	General population	Population cancer registry	NHL, B-cell (and subtypes), T-cell	3 055	18–74	Total NSAIDs	Interview	Frequency and duration (≥5 tablets/month for ≥1 year)	2 years
Doody, 1996 (38)	USA	1958–1982	General population	Hospital discharge records	NHL	94	NA	NA-NSAIDS (phenylbutazone)	Hospital records	Ever used	1, 2, 5, 10, 15, 20 years
Flick,2006 (16)	USA	2001–2004	General population	Population cancer registry	NHL	1000	21–85	Aspirin, NA-NSAIDs, Total NSAIDs	Interview	Frequency and duration (≥2 days/week for ≥3 months)	1 year
Hoeft, 2008 (23)	Germany	1999–2002	General population	Hospitals and office-based physicians	NHL	710	18–80	Total NSAIDs	Interview	Frequency and duration (>1 time/week for ≥1 year)	No
Holly, 1999 & 2003 (19,20)	USA	1988–1995	HIV negative population	Population cancer registry	NHL, B-cell (and subtypes)	1304	21–74	Total NSAIDs	Interview	Duration (≥4 weeks)	1 year
Kato, 2002 (10)	USA	1995–1998	General population (females)	Population cancer registry	NHL, B-cell (and subtypes), T-cell	376	20–79	Aspirin, NA-NSAIDS, Total NSAIDs	Interview	Frequency and duration (daily use for ≥6 months)	1 year (2 years for those interviewed within 1 year of diagnosis)

DOI: 10.1002/hon

Zhang, 2004 (18)	USA	1996–2000	General population (females)	Population cancer registry	NHL, B-cell, T-cell	601	21–84	Aspirin, NA-NSAIDs, Total NSAIDs	Interview	Frequency and duration (>once/day for ≥6 months)	1 year
Zhang, 2006 (12)	USA	1977–2002	Hospital patients	Hospital discharge records	NHL	529	18–79	Aspirin, Total NSAIDs	Interview	Frequency and duration (>4/week for ≥3 months)	1 year
Cohort studies											
Armenian, 1996 (14)	USA	1985–1991	Male AIDS patients	Existing cohort study	NHL	84	NA	Aspirin, Total NSAIDs	Interview	NA	No
Cerhan, 2003 (7)	USA	1992–1999	General population (postmenopausal women)	Population cancer registry	NHL	131	55–69	Aspirin, NA-NSAIDs, Total NSAIDs	Self-completed questionnaire	Frequency	2 years
Erber, 2009 (24)	USA	1993–1996	General population	Population cancer registry	NHL, B-cell (and subtypes)	939	45–75	Aspirin, NA-NSAIDs	Self-completed questionnaire	Frequency and duration (≥2 times/week for ≥1 month)	No
Teras, 2013 (9)	USA	1992–2007	General population	Hospital records, population cancer registry and death registry	NHL, B-cell subtypes	1709	50–74	Aspirin, NA-NSAIDs, Total NSAIDs	Self-completed questionnaire	Dose (>30 regular-dose pills per month)	2 years
Walter, 2011 (17)	USA	2000–2008	General population	Population cancer registry	NHL, B-cell (and subtypes)	577	50–76	Aspirin, NA-NSAIDs, Total NSAIDs	Self-completed questionnaire	Frequency and duration (≥4 days/week for ≥4 years)	No

NHL, non-Hodgkin lymphoma; NA-NSAIDs, non-aspirin non-steroidal anti-inflammatory drugs; NA, not available.

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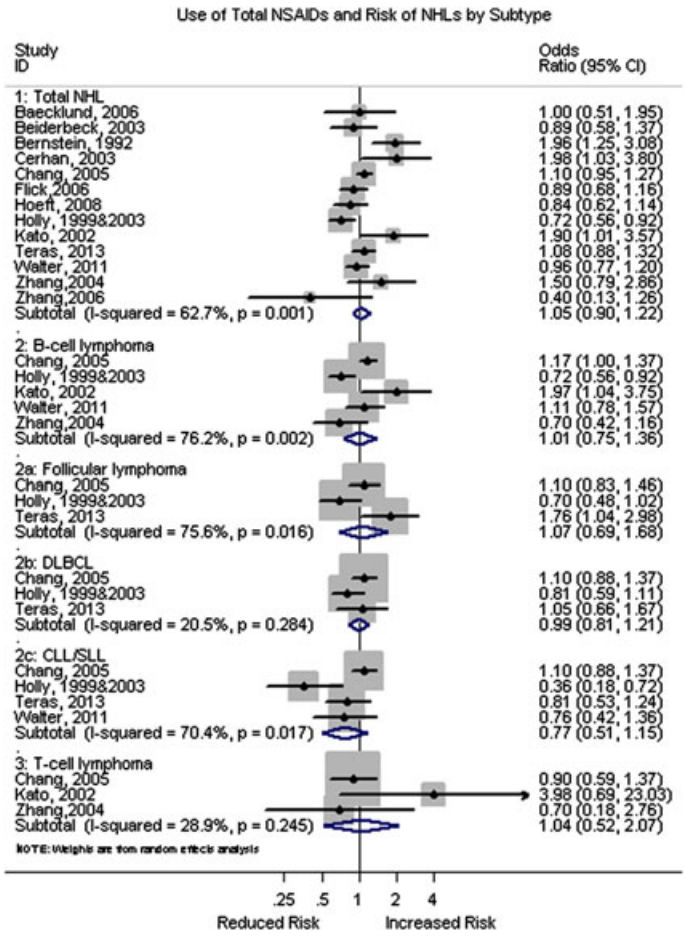

Figure 2. Forest plot of relative risk and pooled odd ratio: use of NSAIDs (as a class) and risk of NHLs by subtype

exception: aspirin use was associated with a reduced risk of CLL/SLL (POR = 0.70, 95% CI 0.54–0.91), and there was no heterogeneity amongst the studies (p for heterogeneity = 0.842, $I^2 = 0.0\%$).

Use of NA-NSAIDs was associated with an increased risk of an NHL diagnosis (POR = 1.33, 95% CI 1.11–1.60), and there was almost no heterogeneity (p for heterogeneity test = 0.342, $I^2 = 11.2\%$), as shown in Figure 4. Limiting the analysis to studies adjusting for medical indications and/or use of other medications showed similar results (data not shown). Further analysis stratified by sex (Figure 5) suggested that this association was stronger amongst females (POR = 1.41, 95% CI 1.01–1.97) than amongst males (POR = 1.16, 95% CI 0.84–1.61), although this analysis was limited by the number of included studies as indicated by the relatively wide confidence intervals. Other study characteristics had no impacts on the pooled estimation.

Discussion

With almost twice the number of studies and included NHL patients, our meta-analysis corroborates the results of a previous meta-analysis that found no evidence for an association between NSAID use and the risk of NHL [22]. In addition, our meta-analysis demonstrated that use of NSAIDs (as a class) was not associated with the risk of several NHL subtypes. However, we found that use of aspirin was associated with reduced risk of CLL/SLL but not with other examined subtypes. On the other hand, use of NA-NSAIDs was associated with increased risk of any NHL diagnosis especially amongst females.

The finding of no association between NSAID use and NHL risk might be real, but could also be a reflection of the limitations of the reviewed studies; all of them were observational in nature and, therefore, are more likely to be subject to bias and confounding. First, most studies examined the effect of NSAID use as a group on the risk of all NHLs grouped together. NHLs are very heterogeneous with respect to their epidemiologic distribution, clinical features, and morphologic and other characteristics [39]. Grouped analyses may have masked significant associations with certain subtypes. However, studying individual subtypes is also challenging due to the complexity and diversity of the classification schemes employed over

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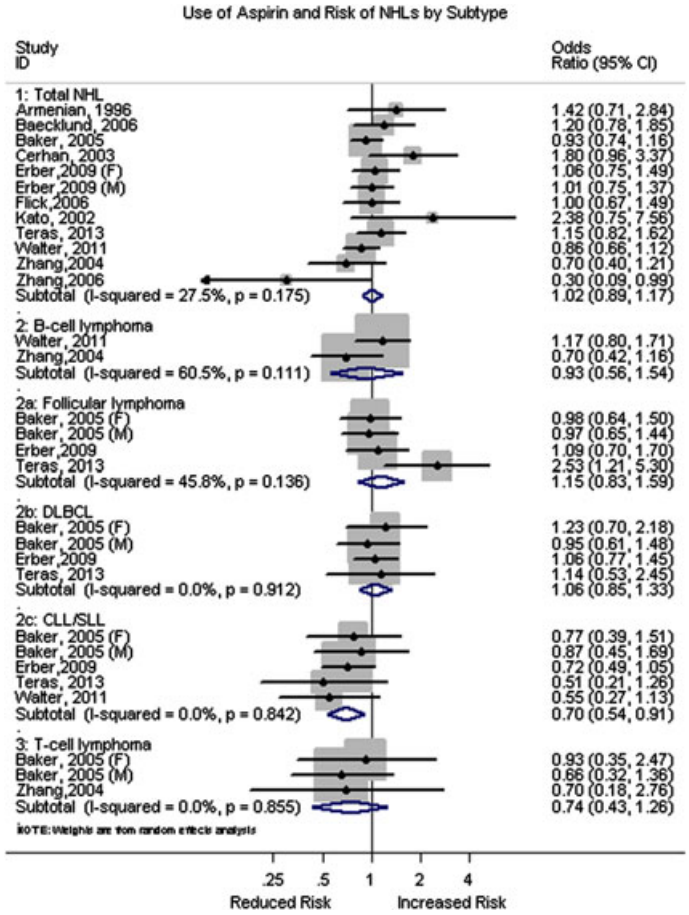

Figure 3. Forest plot of relative risk and pooled odd ratio: use of aspirin and risk of NHLs by subtype

time and the lack of consensus on disease typology [40]. Most studies relied on cancer registration data, which have been shown to differ from expert classification [40]. The resulting disease misclassification is most likely non-differential with respect to NSAID use and could have therefore masked clinically significant associations. However, it is also possible that misclassification is differential if NSAID use was associated with increased likelihood of the diagnosis of asymptomatic or indolent NHL cases, as would be the case if increased use of imaging amongst rheumatoid arthritis patients (who are often heavy NSAID users) was associated with increased detection of some NHLs (screening bias). This kind of measurement error could mask any beneficial effects of NSAID use or even lead to positive association.

Screening bias may explain increased risk of total NHL with NA-NSAID use especially amongst females who are generally at higher risk of autoimmune diseases [41], increasing their chance of receiving diagnostic workup that might result in the diagnosis of coincidental NHL. Generally, NSAID users, particularly regular users, are more likely to access healthcare services compared with non-users [42], resulting in a greater chance of being diagnosed or included in studies. Protopathic bias (reverse causality resulting from increased use of NSAIDs to treat pain resulting from undiagnosed NHL) is another possibility, but most studies have excluded NSAID use occurring immediately (one or more years) prior to NHL diagnosis. Confounding by indication is another possibility as NA-NSAID use is strongly associated with several autoimmune diseases (e.g. rheumatoid arthritis) that have been shown to independently increase NHL risk [43–45]. However, excluding the study involving rheumatoid arthritis patients [11] from the main analysis showed similar results. Although NSAID indications, and sometimes use of co-medications (e.g. immunosuppressants) were adjusted in most studies, residual confounding from these factors cannot be ruled out. Hormone use is another potential confounder, although the association between hormone use and NHL risk amongst women [46] is still very controversial. Furthermore, we are not aware of any direct experimental evidence from animal or laboratory studies supporting the lymphomagenesis initiating or promoting effect of NA-NSAID. Overall, we think that the association between NA-NSAID use and NHL incidence risk is far

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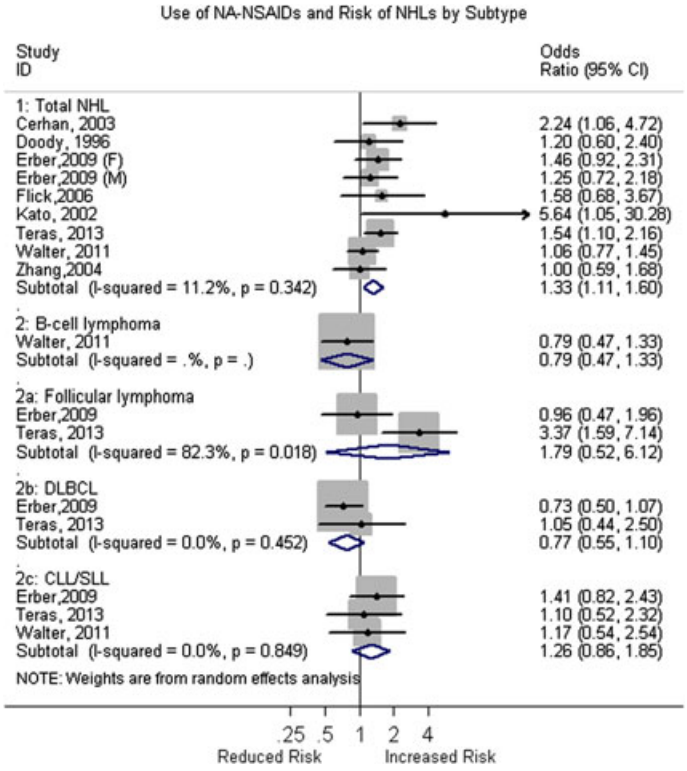

Figure 4. Forest plot of relative risk and pooled odd ratio: use of NA-NSAIDs and risk of NHLs by subtype

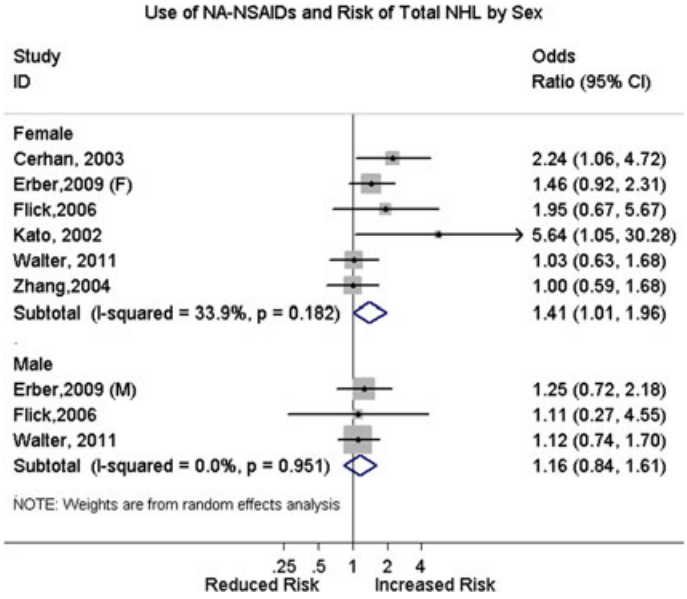

Figure 5. Forest plot of relative risk and pooled odd ratio: use of NA-NSAIDs and risk of total NHL by sex

from conclusive and needs further investigation using both mechanistic and epidemiologic studies.

Exposure to NSAID use was defined differently in reviewed studies which posed challenges to estimating pooled relative risks. Studies have relied on different sources to collect NSAID use information. These sources, however, varied in validity and reliability. Administrative databases contain detailed information on medication use, but typically only include information on a limited period and do not include information on over-the-counter drug use, which can be substantial in the case of NSAIDS [47]. Using interviews and questionnaire, on the other

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hand, is easier to retrospectively collect information on lifetime NSAID use and on both prescription and non-prescription use [48]. When defining exposures to NSAIDs, studies also measured frequency and duration of use differently (Table 1). In addition, most studies did not allow for a long enough latency period for the detection of any carcinogenic or anti-tumour effects. This kind of measurement error tends to be non-differential and, therefore, tends to bias results towards the null.

The number and nature of potential confounders adjusted for in the included studies varied. Whilst database-based studies often adjusted for NSAID indications and co-medications, residual confounding might still exist due, for instance, to misclassification of measured medical conditions. Also, these studies did not have data on other potential confounders such as occupational and lifestyle factors [43,44]. On the other hand, studies that collected that information using interviews or questionnaires might be still subject to residual confounding depending on the quality of the gathered information. Finally, several studies were hospital-based or conducted within specific populations (e.g. AIDS patients, rheumatoid arthritis patients, or postmenopausal women), raising concerns about selection bias and generalizability [10,12].

The association between use of aspirin and reduced risk of CLL/SLL appears to be consistent with the findings of lower risk of several cancers such as colorectal and prostate cancers amongst aspirin users [3,4]. This is an intriguing finding, because most of the sources of bias and confounding (e.g. protopathic bias, screening bias) discussed earlier tend to mask inverse associations. It is still possible that this association is due to a healthy user effect (regular medication users may have healthier lifestyles) or confounding by another medication or supplement. However, there is an increasing body of evidence supporting aspirin's anti-cancer effects, although little is known about hematologic malignancies specifically [49]. Laboratory and animal studies, by showing that aspirin induced CLL tumour cell apoptosis, seem to support the finding [6]. The effects of aspirin may differ from those of other NSAIDs due to differences in pattern of use or pharmacokinetics and pharmacodynamics properties. Although sharing similar mechanism of action, NSAIDs inhibit the cyclooxygenase enzymes, COX-1 and COX-2, differently. Inhibition of COX is considered the primary anti-tumour mechanism of aspirin and other NSAIDs [49]. Unlike other NSAIDs, aspirin permanently inhibits the COX isozymes through irreversible acetylation of the enzymatic active site [50]. The rate of recovery of the tissue, and therefore the duration of effect of administered NSAIDs, depends on the ability of the tissue to regenerate its COX enzymes [51]. Tissues that cannot regenerate the COX enzymes inactivated by aspirin, for example, mature platelets that lack the cellular machinery required for protein synthesis, are particularly susceptible to the effects of aspirin [52]. No specific information is available on the duration of effect of individual NSAIDs on lymphatic tissues. In addition to COX-2 inhibition, other effects including inhibition of angiogenesis, induction of apoptosis, disruption of signal-transduction pathways and inhibition of oxidative DNA damage may also have a role although exact mechanisms are unclear [6]. Overall, more research is needed to replicate this finding.

This analysis has several limitations. First, only published studies have been included. Although no reporting bias was detected in the funnel plot analysis, the possibility cannot be excluded. Second, the analyses (particularly subgroup analyses) were based on a relatively small number of studies with diverse characteristics. Although the random effects model was applied to estimate pooled ORs and subgroup analyses did not support an influential effect for most of study characteristics, these approaches might not have accounted for the heterogeneity introduced by the differences in defining disease and drug use as discussed earlier. Third, there were not enough data to take into account the effects of dose or duration of use. Changes in NSAID use (e.g. type and dose) were not collected in the studies. The findings may not apply to children and adolescents because all reviewed studies were limited to adults only.

In conclusion, epidemiologic evidence for the association between use of NSAIDs and risk of NHL is still inconclusive. The effects of NSAID use on NHL risk may differ by drug type, sex, and NHL subtype. These considerations need to be incorporated in the design of future studies. Given the limitations of current evidence and the high cost of clinical trials, observational studies remain the preferred approach. Future observational studies should endeavour to verify the accuracy of NHL ascertainment and classification; collect detailed information on frequency, dose and duration of NSAID use; allow for a variable latency period; and carefully control for confounders and screening bias. Studies focused on pediatric NHL and on the risk of NHL in developing countries are needed.

Conflict of interest

S. M. M. has received unrestricted research grants from GlaxoSmithKline, Sanofi Pasteur and Pfizer for unrelated studies. S. M. M. was supported by an establishment grant from the Manitoba Health Research Council. S. M. M. is a Canada Research Chair in Pharmaco-epidemiology and Vaccine Evaluation and the Great-West Life, London Life and Canada Life Junior Investigator of the Canadian Cancer Society [grant no. 2011-700644]. None of these sponsors had any role in the design and conduct of the study; analysis and interpretation of the data; or preparation or approval of the manuscript.

DOI: 10.1002/hon

Ethics statement

This analysis did not involve human subjects or animals. No ethical approval is required.

Acknowledgement

The authors thank Dr Songul Bozat-Emre for valuable comments.

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DOI: 10.1002/hon