Aspirin and Other Nonsteroidal Anti-inflammatory Drugs in Relation to Hodgkin Lymphoma Risk in Northern Denmark

Ellen T. Chang1,2, Deirdre P. Cronin-Fenton3, Søren Friis4, Henrik Hjalgrim5, Henrik Toft Sørensen3, and Lars Pedersen3

Abstract

There are few known modifiable risk factors for Hodgkin lymphoma, but the recent finding of an inverse association between routine regular-strength aspirin use and Hodgkin lymphoma risk suggests that aspirin may protect against Hodgkin lymphoma development. To further investigate this association using prospectively collected data, we conducted a population-based case-control study in northern Denmark. A total of 478 incident Hodgkin lymphoma cases were identified in nationwide health-care databases from 1991 to 2008. Ten population controls were matched to each case on age, sex, and county using risk-set sampling. Use of aspirin, selective cyclooxygenase-2 inhibitors, and other nonsteroidal anti-inflammatory drugs (NSAIDs) from 1989 to 2007 was ascertained by linkage to a population-based prescription database. Conditional logistic regression was used to estimate odds ratios for associations between medication use and risk of Hodgkin lymphoma. The odds ratio (95% confidence interval) for ever use (>2 prescriptions) compared with never/rare use (≤2 prescriptions) of low-dose aspirin was 0.7 (0.5-1.2). The association with low-dose aspirin use did not vary appreciably by recentness, duration, or intensity of use. Recent use (>2 prescriptions in the 1-2 years before the index date), short-term use (<7 years), and medium/high-intensity use (≥25% of duration of use covered by prescription) of selective cyclooxygenase-2 inhibitors or other NSAIDs was associated with increased Hodgkin lymphoma risk possibly due to prodromal symptoms among cases. In conclusion, our results provide some evidence of a protective effect of low-dose aspirin, but not other NSAIDs, against Hodgkin lymphoma development.

Introduction

Hodgkin lymphoma is one of the most common cancers of children and young adults in western countries, and it is the third leading cancer in terms of average years of life lost per patient in the United States (1). Few, if any, established Hodgkin lymphoma risk factors are readily modifiable. However, an inverse association between routine regular-strength (325 mg) aspirin use and risk of Hodgkin lymphoma was recently observed in a U.S. population-based case-control study of 565 Hodgkin lymphoma patients and 679 controls (2). Comparing routine users (those who reported using aspirin ≥2 times per week during the last 5 years) with nonroutine users, the odds ratio (OR) of Hodgkin lymphoma was 0.60 [95% confidence interval (95% CI), 0.42-0.85]. This inverse association did not vary by age group, sex, level of education, use of non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, or, among Hodgkin lymphoma patients, by presence of B-symptoms, time interval between diagnosis and interview, or tumor EBV positivity. In the same study, there was no association between routine use of nonaspirin NSAIDs and Hodgkin lymphoma risk.

Distinctive biological properties of aspirin, including irreversible binding to cyclooxygenase-2 (COX-2; ref. 3) and inhibition of proinflammatory transcription factor NF-κB (4, 5), a necessary survival factor for malignant Hodgkin lymphoma cells (6–9), may partially explain the observed inverse association of aspirin but not other NSAIDs with Hodgkin lymphoma risk. To follow up on these findings, we conducted a population-based case-control study with prospectively collected data in northern Denmark to investigate the association of aspirin and other NSAIDs, including selective COX-2 (sCOX-2) inhibitors, with risk of Hodgkin lymphoma.

Materials and Methods

This study included residents of the four former Danish counties of North Jutland, Aarhus, Viborg, and Ringkøbing, which have a combined population of ~1.7 million inhabitants. The Danish National Health Service provides tax-supported health care to all residents...
of the country and refunds part of patient expenditures on
a wide range of prescribed drugs, including NSAIDs and
cSOX-2 inhibitors, the latter of which became available in
Denmark in 1999. All health-related services are regist-
tered to individual patients by use of their civil personal
registration number, assigned to all Danish citizens since
1968. This unique civil personal registration number fac-
ilitates linkage between population-based registries, in-
cluding the Danish Cancer Registry (10), the Danish
National Registry of Patients (11), and countywide pre-
scription databases.

The methods we used have been described elsewhere
(12), with expansion of the study base to the four former
counties for which data have been merged into a research
database at Aarhus University. Briefly, we used the Can-
cer Registry to identify all patients (n = 403) who had a
first diagnosis of Hodgkin lymphoma (International
Classification of Diseases, 10th Revision code C81) starting
on January 1, 1991 in North Jutland County, January 1,
1998 in Aarhus County, and January 1, 2000 in Viborg
and Ringkøbing counties, and continuing through De-
cember 31, 2006 in all four former counties (now
merged into two regions), and we used the National
Registry of Patients (which has more recent data) to as-
certain all patients (n = 75) who had a first diagnosis of
Hodgkin lymphoma within all hospitals in the two re-
gions from January 1, 2007 to December 31, 2008. The
Cancer Registry includes the civil personal registration
number and detailed individual data on all cancer diag-
noses in Denmark since 1943 (10), whereas the Registry
of Patients includes the civil personal registration num-
ber and detailed individual data on all nonpsychiatric
hospital admissions since 1977 and outpatient contacts
since 1995 (11). Until 2003, the Cancer Registry was
based on mandatory notifications by Danish medical
doctors (10); since then, the Cancer Registry has been
based on records from the Registry of Patients, with sec-
ondary histologic confirmation from the National Pa-
thology Registry (13, 14). Within the Danish Civil
Registration System database (15, 16), we performed
risk-set sampling to 10 population controls per case
among living individuals without a history of Hodgkin
lymphoma on the index date (the date of diagnosis for
each case), for a total of 4,780 controls matched on age,
sex, and county of residence.

All pharmacies in the four former counties are
equipped with computerized accounting systems that re-
cord a customer’s civil personal registration number and
prescription data, including type and quantity according
to the Anatomical Therapeutic Chemical Classification
System (17), and date of dispensing at the pharmacy.
This information is transferred electronically to countywide
prescription databases (12, 18). Using these databases (es-

tablished in North Jutland County in 1989, Aarhus Coun-
ty in 1996, and Viborg and Ringkøbing counties in 1998,
thus ensuring a minimum of 2 years of prescription his-
tory in the present study), we identified prescriptions for
low-dose aspirin (75, 100, or 150 mg/tablet; Anatomical
Therapeutic Chemical codes B01AC06 and N02BA01),
high-dose aspirin (500 mg/tablet; Anatomical Therapeu-
tic Chemical codes N02BA51 and N02BA01), cSOX-2 in-
hibitors (Anatomical Therapeutic Chemical codes
M01AH01, M01AH, M01AH03, M01AH05, M01AC05,
M01AB05, and M01AC06), and other NSAIDs (remaining
Anatomical Therapeutic Chemical codes within group
M01A). We excluded prescriptions within 1 year of the
index date to reduce any potential effect of subclinical
disease on medication use.

We defined “ever users” of a medication as individuals
who had >2 prescriptions and “never/rare users” as
those who had ≤2 prescriptions. The average length of
a prescription was 30 days. Ever users were further di-
vided into recent users (those who had >2 prescriptions
during the period 1-2 years before the index date) and
former users (>2 prescriptions overall but ≤2 during the
recent period). Duration of use was classified as long-
term (≥7 years) or short-term (<7 years) based on the
number of days between the first and the last pre-
scriptions plus the duration of the last prescription.
Inten-
sity of use was defined as low (<25%) or medium/high
(≥25%) according to the number of days of prescription
coverage divided by duration of use in days (12).

To obtain a nonspecific proxy for chronic NSAIDs use,
we identified subject comorbidities before the index date
using inpatient and outpatient data from the Registry of
Patients. Comorbidities were summarized using Deyo’s
adaptation of the Charlson index (19, 20). In addition, be-
cause connective tissue disorders in particular (e.g., rheu-
matoid arthritis, which is associated with both greater
NSAIDs use and higher Hodgkin lymphoma risk; refs.
21, 22) may confound the associations of interest, we iden-
tified connective tissue disorders before the index date.

We used conditional logistic regression to compute
ORs (95% CIs), matching on age, sex, and former county
of residence, and additionally adjusting for Charlson in-
dex (0, 1-2, or ≥3 comorbidities). Further adjustment for
connective tissue disorders did not affect the results (data
not shown). Because the etiology of Hodgkin lymphoma
varies by age (23), we stratified the results by age (<40
versus ≥40 years) and performed Wald tests for interac-
tions between medication use and age group. In all anal-
yses, never/rare users (≤2 prescriptions) comprised the
reference group. Given the risk-set sampling of controls,
the ORs are estimates of the incidence rate ratios in the
underlying population.

Results

The distribution of Hodgkin lymphoma cases and
matched controls is shown in Table 1. Ever use of low-
dose aspirin was associated with 30% lower risk of Hodg-
kin lymphoma (95% CI, −50% to +20%), but the estimate
was statistically nonsignificant, as were the estimates for
former and recent use, short-term and long-term use, and
low-intensity and medium/high-intensity use as well as
ever use of high-dose aspirin (Table 2). When low-dose
Aspirin use was classified according to both intensity and duration of use (short-term, low intensity; short-term, high intensity; long-term, low intensity; or long-term, medium/high intensity), the lowest ORs were found in association with short-term, low-intensity use (OR, 0.5; 95% CI, 0.2-1.3) and long-term, medium/high-intensity use (OR, 0.7; 95% CI, 0.5-1.2). The inverse association between use of low-dose aspirin and Hodgkin lymphoma risk was apparent only among never/rare users of nonaspirin NSAIDs (OR, 0.6; 95% CI, 0.3-1.0) and not among ever users of nonaspirin NSAIDs (OR, 1.0; 95% CI, 0.5-1.9). When the analysis was restricted to individuals with at least 7 years of prescription history, the estimates of association with use of low-dose aspirin and nonaspirin NSAIDs, including duration of use, did not change substantially (data not shown). Likewise, when we limited the analysis to Hodgkin lymphoma patients included in the Danish Cancer Registry (1991-2006; n = 403) or when we excluded prescriptions within 2 years of the index date, the results were unchanged (data not shown).

In an exploratory analysis stratified by age group (<40 versus ≥40 years), we found that only one control and no Hodgkin lymphoma cases ages <40 years were ever users of low-dose aspirin. Therefore, the association with low-dose aspirin use could be estimated only among subjects ages ≥40 years (OR, 0.8; 95% CI, 0.5-1.2). The association with ever use of sCOX-2 inhibitors or other NSAIDs did not vary between younger adults (OR, 1.1; 95% CI, 0.7-1.8) and older adults (OR, 1.3; 95% CI, 1.0-1.8; \( \phi_{\text{heterogeneity}} = 0.58 \)). Likewise, there was no variation by age group in the association with use of low-dose aspirin use or use of sCOX-2 inhibitors alone (OR for <40 years, 0.9; 95% CI, 0.3-2.2; OR for ≥40 years, 1.1; 95% CI, 0.7-1.8; \( \phi_{\text{heterogeneity}} = 0.62 \)) or ever use of other NSAIDs alone (OR for <40 years, 1.4; 95% CI, 0.9-2.4; OR for ≥40 years, 1.1; 95% CI, 0.8-1.6; \( \phi_{\text{heterogeneity}} = 0.43 \)).

**Table 1. Distribution of Hodgkin lymphoma cases and matched controls in northern Denmark, 1991-2008**

<table>
<thead>
<tr>
<th></th>
<th>Cases (( n = 478 ))</th>
<th>Controls (( n = 4,780 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>58 (12)</td>
<td>582 (12)</td>
</tr>
<tr>
<td>20-29</td>
<td>82 (17)</td>
<td>812 (17)</td>
</tr>
<tr>
<td>30-39</td>
<td>101 (21)</td>
<td>1,024 (21)</td>
</tr>
<tr>
<td>40-49</td>
<td>56 (12)</td>
<td>554 (12)</td>
</tr>
<tr>
<td>50-59</td>
<td>44 (9)</td>
<td>430 (9)</td>
</tr>
<tr>
<td>60-69</td>
<td>66 (14)</td>
<td>678 (14)</td>
</tr>
<tr>
<td>≥70</td>
<td>71 (15)</td>
<td>700 (15)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>198 (41)</td>
<td>1,980 (41)</td>
</tr>
<tr>
<td>Male</td>
<td>280 (59)</td>
<td>2,800 (59)</td>
</tr>
<tr>
<td><strong>County of residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North Jutland</td>
<td>197 (41)</td>
<td>1,970 (41)</td>
</tr>
<tr>
<td>Aarhus</td>
<td>184 (38)</td>
<td>1,840 (38)</td>
</tr>
<tr>
<td>Viborg/Ringkoebing</td>
<td>97 (20)</td>
<td>970 (20)</td>
</tr>
<tr>
<td><strong>Charlson comorbidity index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>354 (74)</td>
<td>4,146 (87)</td>
</tr>
<tr>
<td>1-2</td>
<td>108 (23)</td>
<td>563 (12)</td>
</tr>
<tr>
<td>≥3</td>
<td>16 (3)</td>
<td>71 (1)</td>
</tr>
<tr>
<td><strong>Connective tissue disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>461 (96)</td>
<td>4,718 (99)</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (4)</td>
<td>62 (1)</td>
</tr>
</tbody>
</table>

Consistent with earlier observations (2), we found an inverse association between use of low-dose aspirin and risk of Hodgkin lymphoma in this study. Although the association was statistically nonsignificant, the OR estimate of 0.7 is comparable with the previously reported point estimate of 0.6 for use of ≥2 regular-strength tablets/wk, on average, versus <2 tablets/wk during the preceding 5 years (2). The inverse association was limited to adults ages ≥40 years, although we could not rule out an association among younger adults. In the earlier study (2), aspirin use was inversely associated with Hodgkin lymphoma risk among both younger and older adults.

We also detected positive associations with recent use of other NSAIDs and short-term, medium/high-intensity use of nonaspirin NSAIDs (including sCOX-2 inhibitors) but no association with long-term or low-intensity use. Although we excluded prescriptions within 1 year of the index date (and, in a secondary analysis, prescriptions within 2 years of the index date), the observed positive associations may nevertheless be due to use of nonaspirin NSAIDs to treat prodromal symptoms (including fever and swollen lymph nodes) among Hodgkin lymphoma cases. It is possible that the inverse association of Hodgkin lymphoma risk with use of low-dose aspirin, particularly among never/rare users...
of nonaspirin NSAIDs, as well as the positive association with recent or short-term, medium/high-intensity use of nonaspirin NSAIDs, were due to switching from aspirin to other NSAIDs to treat symptoms before Hodgkin lymphoma diagnosis. However, we lacked a large enough sample to examine this question in detail. Our previous cohort analysis of prescription data in North Jutland County revealed no association between nonaspirin NSAIDs use and Hodgkin lymphoma risk (based on 23 cases; ref. 24) but had insufficient case numbers to study the association between low-dose aspirin use and Hodgkin lymphoma risk (25). To our knowledge, no other studies have examined the association between NSAIDs use and Hodgkin lymphoma risk.

The possible biological mechanisms underlying our findings are not clear, but aspirin inhibits the transcription factor nuclear NF-κB (4, 5), which regulates the expression of genes involved in immune activation, inflammation, cell growth, and apoptosis (4, 26). Constitutively active NF-κB is detected in virtually all malignant Hodgkin lymphoma cells (6), and NF-κB inactivation causes spontaneous apoptosis of those cells (8, 9). Thus, NF-κB appears to play a vital role in Hodgkin lymphoma cell survival (7), and medications

<table>
<thead>
<tr>
<th>Medication use</th>
<th>Cases (n = 478)</th>
<th>Controls (n = 4,780)</th>
<th>OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Low-dose aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rare†</td>
<td>447 (94)</td>
<td>4,495 (94)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Ever†</td>
<td>31 (6)</td>
<td>285 (6)</td>
<td>0.7 (0.5-1.2)</td>
</tr>
<tr>
<td>Former‡</td>
<td>7 (1)</td>
<td>81 (2)</td>
<td>0.6 (0.2-1.3)</td>
</tr>
<tr>
<td>Recent‡</td>
<td>24 (5)</td>
<td>204 (4)</td>
<td>0.8 (0.5-1.3)</td>
</tr>
<tr>
<td>Short duration§</td>
<td>26 (5)</td>
<td>248 (5)</td>
<td>0.7 (0.5-1.2)</td>
</tr>
<tr>
<td>Long duration§</td>
<td>5 (1)</td>
<td>37 (1)</td>
<td>0.9 (0.3-2.6)</td>
</tr>
<tr>
<td>Low intensity†</td>
<td>8 (2)</td>
<td>82 (2)</td>
<td>0.6 (0.3-1.4)</td>
</tr>
<tr>
<td>Medium/high intensity†</td>
<td>23 (5)</td>
<td>203 (4)</td>
<td>0.8 (0.5-1.3)</td>
</tr>
<tr>
<td>High-dose aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rare†</td>
<td>477 (100)</td>
<td>4,776 (100)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Ever†</td>
<td>1 (0.2)</td>
<td>4 (0.1)</td>
<td>1.6 (0.2-14.7)</td>
</tr>
<tr>
<td>sCOX-2 inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rare†</td>
<td>445 (93)</td>
<td>4,504 (94)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Ever†</td>
<td>33 (7)</td>
<td>276 (6)</td>
<td>1.1 (0.7-1.6)</td>
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<tr>
<td>Other NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rare†</td>
<td>405 (85)</td>
<td>4,187 (88)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Ever†</td>
<td>73 (15)</td>
<td>593 (12)</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>sCOX-2 inhibitors or other NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never/rare†</td>
<td>372 (78)</td>
<td>3,946 (83)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Ever†</td>
<td>106 (22)</td>
<td>834 (17)</td>
<td>1.3 (1.0-1.7)</td>
</tr>
<tr>
<td>Former‡</td>
<td>79 (17)</td>
<td>655 (14)</td>
<td>1.3 (0.9-1.7)</td>
</tr>
<tr>
<td>Recent‡</td>
<td>27 (6)</td>
<td>179 (4)</td>
<td>1.6 (1.0-2.5)</td>
</tr>
<tr>
<td>Short duration§</td>
<td>84 (18)</td>
<td>595 (12)</td>
<td>1.5 (1.1-1.9)</td>
</tr>
<tr>
<td>Long duration§</td>
<td>22 (5)</td>
<td>239 (5)</td>
<td>0.9 (0.6-1.5)</td>
</tr>
<tr>
<td>Low intensity†</td>
<td>67 (14)</td>
<td>598 (13)</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>Medium/high intensity†</td>
<td>39 (8)</td>
<td>236 (5)</td>
<td>1.8 (1.2-2.6)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, county of residence, and Charlson index.
†Never/rare use: ≤2 prescriptions total; ever use: >2 prescriptions total.
‡Recent use: >2 prescriptions within the period 1-2 y before index date; former use: >2 prescriptions overall but ≤2 during the recent period.
§Short-term use: <7 y between first prescription and end of last prescription; long-term use: ≥7 y between first prescription and end of last prescription.
∥Low intensity: <25% prescription coverage during total duration of use; high intensity: ≥25% prescription coverage during total duration of use.
that target NF-κB may protect against Hodgkin lymphoma development. In addition, aspirin is unique among the NSAIDs in that it binds irreversibly to the active site of COX-2 (3), the proinflammatory enzyme targeted by standard NSAIDs and sCOX-2 inhibitors (27). These differences between aspirin and other NSAIDs may underlie the inverse association of aspirin alone with risk of Hodgkin lymphoma in the current and previous studies (2).

Unique strengths of the present study include the use of prospectively collected, continuously updated, accurate information on drug prescriptions for up to 18 years. In addition, our current findings are strengthened by the population-based study design and valid, complete ascertainment and follow-up of incident Hodgkin lymphoma (10, 28). Our study included a relatively large number of patients with a disease as uncommon as Hodgkin lymphoma; however, the sample size was nevertheless modest, leading to imprecise OR estimates. Our study is also limited by the lack of information on compliance with prescriptions, indications for prescriptions, and over-the-counter use of aspirin and other NSAIDs. The vast majority of aspirin prescriptions in Denmark are for low-dose aspirin to treat or prevent cardiovascular disease (e.g., thrombosis prevention; ref. 25). Although low-dose aspirin (≤150 mg) and ibuprofen (200 mg) are available without a prescription, the government refunds 50% of costs at the time of prescription, making it likely that we identified most patients using these medications under physician guidance (25). Over-the-counter use of nonaspirin NSAIDs in Denmark accounts for only 14% of total use (29), but over-the-counter use may be more common among individuals without prescriptions than those with prescriptions, leading to an underestimation of any association with Hodgkin lymphoma risk.

Over-the-counter use may also be more common among individuals of high socioeconomic status, among whom Hodgkin lymphoma risk is elevated (30), further diminishing any inverse association with risk. Without detailed information on individual characteristics and exposures, we were unable to adjust for potential confounding by socioeconomic status and other risk factors.

In summary, our observation of a statistically nonsignificant inverse association between aspirin use and Hodgkin lymphoma risk is consistent with, although not entirely confirmatory of, earlier findings. Thus, routine aspirin use remains a theoretically promising means of reducing Hodgkin lymphoma risk. Additional studies with similar prospective, validated data on aspirin use, and ideally with a larger sample size, are needed to establish whether this promise translates into a true protective effect.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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