Lack of Association between Using Aspirin and Development of Non-Hodgkins Lymphoma: A Meta-analysis

Maria Cheraghi1*, Neda Amoori2*, Hosein Fallahzadeh3, Hossein Rahmani4

Abstract

Background: Non-Hodgkins lymphoma (NHL) is a heterogeneous group of malignancies, originating in the lymphatic organs, whose incidence is increasing in developed as well as developing countries. Epidemiological evidence suggests that aspirin may reduce the incidence and mortality of several cancers. The main objective of this study was to evaluate the potential relationship between using aspirin and development of NHL with a meta-analysis. Materials and Methods: A total of 7 studies were included. Outcome was calculated and reported as odds ratios (ORs). Heterogeneity was assessed with Cochrane Q and I^2 statistics. Dissemination bias was evaluated by funnel plot visualization and trim-and-fill analysis. Results: Our analysis showed OR of developing NHL overall of 1 (95% CI: 0.87-1.16, p=0.9), and in females this was 0.81 (95%CI: 0.72-0.92, p=0.001) and in males 1.01 (95%CI: 0.82-1.26, p=0.86). The odds ratio (OR) of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) was 0.85 (95% CI: 0.75-0.97, p=0.02), The ORs of follicular lymphoma (FL) and large B-cell lymphoma (DLBCL) in individuals exposed to aspirin were 1.12 (95% CI: 0.86-1.45, p=0.37) and 1.03 (95% CI: 0.9-1.19, p=0.6) respectively. Conclusions: In conclusion, individuals taking aspirin do not demonstrate any change in risk of Non-Hodgkins lymphoma.

Keywords: Non-Hodgkins lymphoma - aspirin - meta-analysis - negative influence
studies, non-steroidal, corticosteroids, and NSAIDs. In addition, reference lists were also reviewed manually. The latest research was performed on October 2014.

**Inclusion and exclusion criteria**

In order for articles to be included in our study, the following criteria must be met: 1) case-control or cohort studies; 2) evaluating the relationship between taking Aspirin and the NHL; 3) providing raw data, or relevant information which could be used to calculate an odds ratios (ORs) with 95% confidence intervals (CI). The exclusion criteria included: 1) repeated reports; 2) case reports, editorials, review articles, conference papers and meta-analysis.

**Data extraction and synthesis**

All publications retrieved from the databases were examined by two independent reviewers (Maria Cheraghi and Neda Amoori) and disagreements were solved by researcher Hosein Fallahzadeh. For each eligible study, the following characteristics were collected: first author, year of publication, Area, study design, Source of case, sources of control, Ascertainment measure, Adjustment factor.

**Statistics and analysis**

Meta-analysis using Comprehensive Meta Analysis (v.2.0; Biostat, Englewood, NJ, USA) software was conducted. All results were reported at the pooled ORs and 95% CI. To measure the effect of exposure on the outcome studied, measurements “Relative Risk (RR)”, “Attributable Risk (AR)”, and Hazard Ratio (HR)” in cohorts studies, and “Odds Ratio (OR)” in case-control studies were applied. To evaluate qualitatively heterogeneous data, the chi-square test was used in confidence level of 10% (p<0.1). The test “I^2” (Higgins et al., 2003) was used to assess quantitative heterogeneity in the results so that if I^2 is greater than 50%, heterogeneity will be severe. To estimate the variances between studies, the statistical method “tau-squared” was applied. Statistical models like fixed effect or Mantel Haenszel, and random effect (REM) or Dersimonian-laird were used for the analysis and integration of results. REM was calculated to determine heterogeneity of studies. Publication bias was assessed by Begg’s funnel plot. Forest plots were drawn to compare the extracted parameters from the studies.

**Results**

**Literature search**

A total of 7 published articles regarding the relationship between taking Aspirin, and NHL the NHL were identified by applying the inclusion criteria (Figure 1) (Kato et al., 2002; Erber et al., 2009; Teras et al., 2013; Flick et al., 2006; Cerhan et al., 2003; Zhang et al., 2006; Baker et al., 2005) and 3 articles reported intake red meat and risk subtype NHL (Erber et al., 2009; Teras et al; Baker et al., 2005).

**Study characteristics**

The main characteristics of the 7 studies are as follows, of which 4 were population-based case-control studies

![Figure 1. Flow Chart of Study Selection](image)

![Figure 2. Forest Plot of Odds Ratio Estimates of NHL for Persons who Received Aspirin](image)

![Figure 3. Funnel Plot of Studies of NHL Risk After Aspirin Exposure](image)
and 3 were cohort study. Eleven studies were published between 2002 and 2013 and involved 5308 cases and 9086 controls. More details of these studies are summarized in Table 1.

**Results of meta-analysis**

Using the random-effect model, meta-analysis was showed was not a significant association between the taking Aspirin and NHL risk (OR=1.0, 95%CI: 0.87-1.16, p=0.9), the forest plot was shown in Figure 2. The publication bias among studies of intake and NHL risk was not appreciable based on funnel plots (Figure 3).

Outcome of three studies has evaluated in female participants. The NHL risk in females was 0.81 (95%CI top: 0.72-.92, p=0.001). Three studies evaluated outcomes in male participants. The NHL risk in males was 1.01 (95%CI bottom: 0.82-1.26, p=0.86) (Figure 4).

**Taking aspirin and sub group NHL risk**

Analysis using the available data of taking Aspirin also

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Table 1. Characteristics of the Studies Correlating with the Effects Exposure Aspirin on NHL Risks

<table>
<thead>
<tr>
<th>NO</th>
<th>Study(ref.)</th>
<th>Area</th>
<th>Source of case</th>
<th>Source of controls</th>
<th>Ascertainment measure</th>
<th>Adjustment factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Flick et.al,2006</td>
<td>California</td>
<td>Northen California cancer centers SEER,415</td>
<td>Population controls sampled by random digit dialing and from medical services file.501</td>
<td>Face to face interviews</td>
<td>Age, sex, residence</td>
</tr>
<tr>
<td>2</td>
<td>Zhang et.al,2006</td>
<td>USA</td>
<td>Newly hospitalized patients, in Newyork, philadelphia, Boston and baltimore,529</td>
<td>Population controls selected hospitalized patients, in Newyork, philadelphia, Boston and baltimore,2013</td>
<td>Interview</td>
<td>Age, sex, study center, year of interview</td>
</tr>
<tr>
<td>3</td>
<td>Baker et.al,2005</td>
<td>Newyork</td>
<td>Buffalo country cancer registry</td>
<td>Population controls sampled by random digit dialing and from medical services file.2512</td>
<td>Questionnaire</td>
<td>Sex, age</td>
</tr>
<tr>
<td>4</td>
<td>Kato et.al,2002</td>
<td>Newyork</td>
<td>Cancer registry in the upstate counties of new York state(NYS)</td>
<td>Control selected from random sample from the NYS Department of Motor vehicles license file(DMV)</td>
<td>Telephone interviews</td>
<td>Age</td>
</tr>
<tr>
<td>5</td>
<td>Cerhan et.al,2003</td>
<td>United state</td>
<td>Iowa death certificate and cancer registry file</td>
<td>Iowa women health study</td>
<td>Mailed questionnaire</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Erber et.al,2009</td>
<td>United state(Los Angeles, Hawaii)</td>
<td>Hawaiitumor registry Los Angeles country cancer surveillance program, state of California cancer registry</td>
<td>Mutilithic cohort(MEC) study</td>
<td>Mailed questionnaire</td>
<td>Ethnicity, education, body mass index and alcohol intake</td>
</tr>
<tr>
<td>7</td>
<td>Teras et.al,2013</td>
<td>United state</td>
<td>Cancer self report,medical records and state cancer registry</td>
<td>Cps-2 Nutrition cohort study</td>
<td>Mailed questionnaire</td>
<td>NR</td>
</tr>
</tbody>
</table>

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Table 2. Analysis of Taking Aspirin and NHL Risk

<table>
<thead>
<tr>
<th>variable</th>
<th>No. of studies</th>
<th>Odds ratio</th>
<th>Model</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>95%CI</td>
<td>P</td>
<td>P(%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>7</td>
<td>1.09(0.87-1.16)</td>
<td>0.9</td>
<td>Random</td>
</tr>
</tbody>
</table>
Table 3. Analysis of Taking Aspirin and Subgroup NHL Risk

<table>
<thead>
<tr>
<th>Subgroups NHL</th>
<th>No. of studies</th>
<th>Odds ratio</th>
<th>Model</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>95% CI</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>3</td>
<td>0.85(0.75-0.97)</td>
<td>0.02</td>
<td>Fixed</td>
</tr>
<tr>
<td>FL</td>
<td>3</td>
<td>1.04(0.90-1.21)</td>
<td>0.24</td>
<td>Fixed</td>
</tr>
<tr>
<td>DLBCL</td>
<td>3</td>
<td>1.03(0.90-1.19)</td>
<td>0.6</td>
<td>Fixed</td>
</tr>
</tbody>
</table>

revealed no statistical significant association between: (a) Diffuse large B-cell lymphoma (DLBCL) (OR=1.03, 95%CI:0.9-1.19, p=0.6); (b) Follicular lymphoma (FL) (OR=1.12, 95%CI: 0.86-1.45, p=0.37) and showed no statistical significant association between lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (OR=0.85, 95%CI: 0.86-1.45, p=0.37) (Figure 5). The results are shown in Tables 2 and Table 3.

Discussion
In this study, there was evidence indicated that there was not a significant association between exposure to aspirin and developed NHL. Also, according to analysis of subgroups, a statistically significant difference was observed in the effect of taking aspirin in women suffered from NHL. There was a relation between gender, exposure to aspirin, and NHL. There was a strong statistical association was seen between taking aspirin and the risk of chronic lymphocytic leukemia in different subtypes.

Cerhan et al evaluated the association between taking aspirin and other Non-steroidal drugs, and risk of NHL in post menopausal women with a history of rheumatoid arthritis (RA). The NHL risk (RR) was 1.1.71 in those who were only taking aspirin (95%CI: 0.94-3.13) while RR was 2.39 in those who were taking NSAIDs (95%CI: 1.18-4.83). The result showed that the use of NSAIDs, including aspirin, has been associated with increasing the risk of NHL. However, this association was independent of RA history, and effects of NSAIDs and aspirin were same in RA and non RA Populations(Cerhan et al., 2003). In contrast, Smedby et al determined that the increased risk of NHL was seen in patients with RA (OR: 1.5, 95%CI: 1.1-1.9) so that individuals who are not suffering from RA are not suffering from NHL (Chang et al., 2005). This can likely be due to the effects of modification or confounding factors. New evidence has shown; the importance of NHL severity in autoimmune diseases such as RA. The nested case control study has developed the strongest evidence for this association, and RR of developing NHL in patients with AR was 71 (95%CI: 24-211) (Baeklund et al., 2006).

Other studies suggest that after adjusting severity of NHL, the possible association seem less between RA medication and the lymphoma risk. Setoguchi et al reported that after the data of publication or the size of the study, produce results nearly identical to the primary result.

In conclusion, new information was obtained about the relation between exposure to aspirin and the NHL, as follows:

i) Obtaining a summary of data on estimating odds ratio, risk ratio, and the hazard ratio according to the effect of aspirin on NHL.

ii) No statistically significant effect of aspirin on the NHL.

iii) Significant direct correlation between the effects of aspirin and incidence Diffuse large B-cell lymphoma (DLBCL).

iv) Identifying the impact of different variables on the relation between aspirin use and NHL, such as: studies design, quality of studies, and duration of treatment.

In Conclusion, in this study, finding has shown in those patients who had taken aspirin was not appearing to independently increase risk of Non-Hodgkins lymphoma.

References


