RESEARCH ARTICLE

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

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Abstract

<u>Background</u>: **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.** <u>Materials and Methods</u>: **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.** <u>Results</u>: **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-.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.** <u>Conclusions</u>: **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

Introduction

Non-Hodgkins lymphoma (NHL) is a heterogeneous group of malignancies that originates in the lymphatic organs (Zelenetz et al., 2010; Sangrajrang et al., 2011; Amanat et al., 2013). NHL is the seventh most common cancer and the sixth leading cause of death from cancer in USA (Hernandez et al., 2010; Amoori et al., 2014). Mortality rate of this type of cancer has substantially increased (Clarke et al., 2002; Zekri et al., 2013) in developed countries as well as developing countries and will double every 20 years (Devesa et al., 1992; Broccia et al., 2001) It more occurs because of malfunction of immune system, including primary immunodeficiency syndromes, immunosuppressive drugs for transplant patients, and the immunodeficiency human virus (HIV) (Ansell et al., 2005; Yildirim et al., 2013). Other effective factors are rheumatoid arthritis, diabetes mellitus, overweight (Baecklund et al., 2006; Setoguchi et al., 2006; Hoshida et al., 2007) a history of allergy, family history of cancer (Baecklund et al., 2006; Goldin et al., 2009), taking drugs, such as phenytoin and chemotherapy (Chang et al., 2005; Karami et al., 2014), and exposure

to pesticides, especially phenoxy herbicides (Boffetta et al., 2007; Chia et al., 2012) has been increased risk of NHL. The evidence suggests that aspirin may reduce the incidence and mortality of several cancers (Rothwell et al., 2011; Rothwell et al., 2012). And it has been shown to have a protective effect for colorectal cancer (Thun et al., 2012; Amoori et al., 2014). However, there was not a stable relation between taking drugs as Non-steroidal Anti Inflammatory (NSAISs), including aspirin, and NHL. Therefore, we performed a meta-analysis study to evaluate the potential relationship between using aspirin and the development of NHL.

Materials and Methods

Literature and search strategy

We searched PubMed, Cochrane Library, Medline, and Science Citation Index Expanded databases for case-control and cohort studies on taking Aspirin, and NHL in English. The following search terms were used: (Non-hodgkins lymphoma, NHL, Aspirin, Folicular lymphoma, FL, Diffuse large Bcell, DLBCL, Cronic lymphocytic leukemia, CLL/SLL, cohort, case control, observational

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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 "I²" (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 taking aspirin 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 4were population-based case-control studies
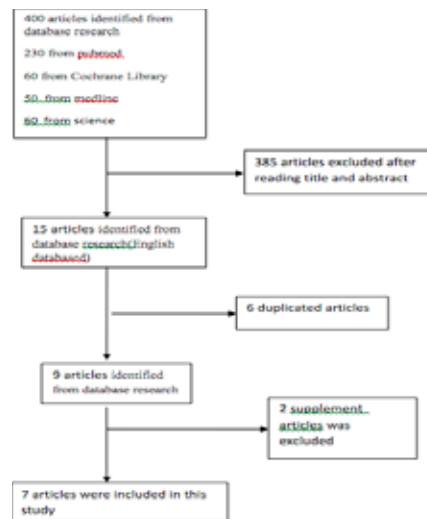

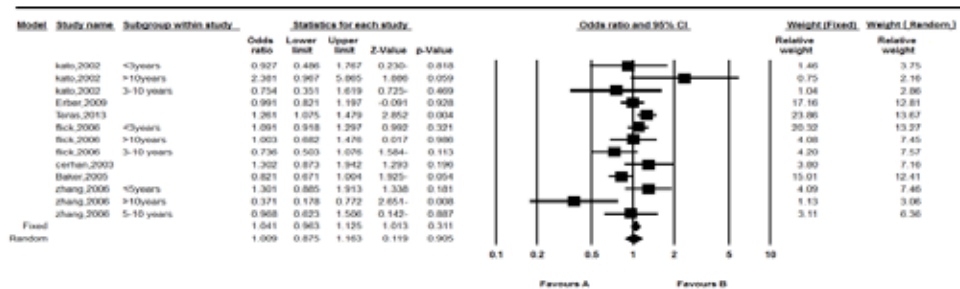**Figure 1. Flow Chart of Study Selection**

Figure 2. Forest Plot of Odds Ratio Estimates of NHL for Persons who Received Aspirin
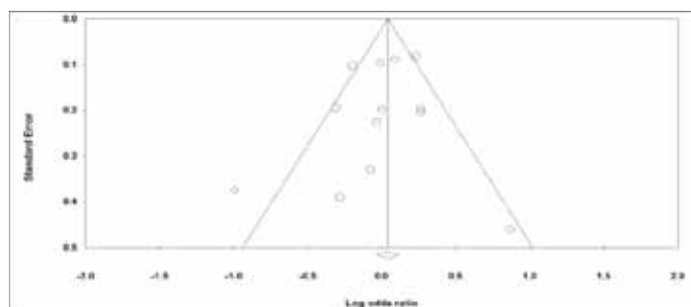

Figure 3. Funnel plot of studies of NHL risk after aspirin exposure

and3 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

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

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

Table 2. Analysis of Taking Aspirin and NHL Risk

variable	No. of studies	Odds ratio		Model	Heterogeneity	
		95%CI	P		I²(%)	P
Aspirin	7	1.09(0.87-1.16)	0.9	Random	59	0.004

100.0

6.3   10.1   20.3

Table 3. Analysis of Taking Aspirin and Subgroup NHL Risk

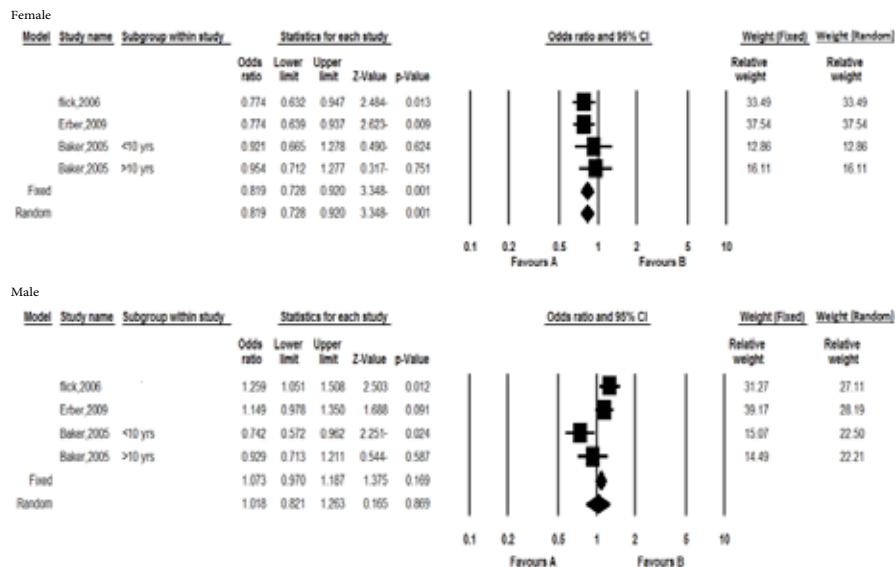| Subgroups NHL	No. of studies	Odds ratio		Model	Heterogeneity	
		95%CI	P		I^2 (%)	P
CLL/SLL	3	0.85(0.75-0.97)	0.02	Fixed	39	0.17
FL	3	1.04(0.90-1.21)	0.24	Fixed	55	0.08
DLBCL	3	1.03(0.90-1.19)	0.6	Fixed	0	0.75

Figure 4. Risk Estimates of the Odds Ratio of Developing NHL for Persons who Received Aspirin, by Sex
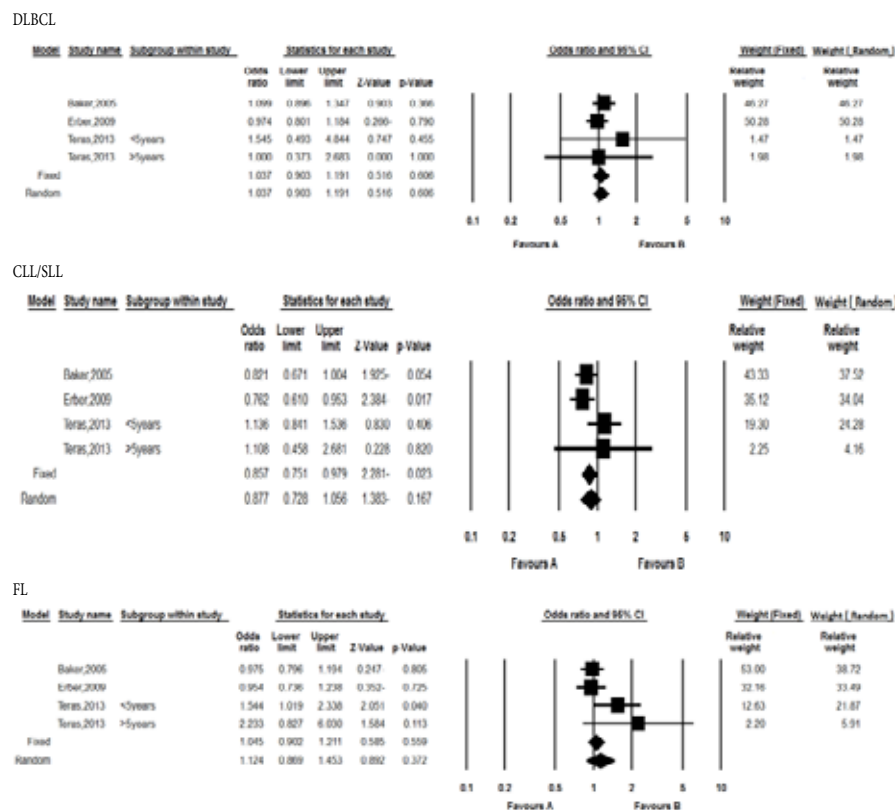

Figure 5. Risk Estimates of the Odds Ratio of Developing NHL for Persons who Received Aspirin, by Lymphoma Subtype. FL indicates follicular lymphoma. DLBCL, Diffuse large B-cell lymphoma and CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma

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) (Baecklund 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 adjusting severity of NHL the relative risk of developing the types of leukemia (haematological) is almost the same in the recipients of the drugs as the anti-tumournecrosis factor (TNF) or Methotrexate (Setoguchi et al., 2006). A study indicated that in persons who taking NSAIDs or NNAS (Non-nacrotic analagesis) over 10 years compared to those who not taking such drugs, the risk of NHL is almost twice (OR: 1.9, 95%CI: 1.01-3.57). Also, various drugs were evaluated based on their length. Many evidences showed a relation between the length of taking drugs (over 10 years) and Ibuprofen. However, there was no significant relation between duration of taking aspirin and the risk of NHL (Kato et al., 2002). In contrast, another study indicated that in individuals who not taking NSAIDs, the adjusted OR has decreased among men and women, but estimating the adjusted OR was null among aspirin users except women. Also, in female who taking aspirin between 3 and less than 9 years reducing the risk of NHL was reported nearly 59% (Flick et al., 2006). A study determined that a significant association was not observed between the use of NSAIDs and NHL while the risk of follicular lymphoma (of NHL subgroups) has been increased (HR: 1.87, 95%CI: 1.08-3.24) (Teras et al., 2013).

Data from surveillance, epidemiology, and End results program has shown that the age standardized incidence rates of NHL has increased 3 to 4% annually from 1970 to 1980s (Ekstrom et al., 2006). Since 1991 the annual increase in the incidence was 0.4% and 1.2% respectively in men and women (Siegel et al., 2011).

Limitation In this meta-analysis, there were a number of limitations and potential bias. First, it seemed that 4 studies had the inclusion criteria, but it was not possible to access the full-texts of them. This may increase the likelihood of selection bias. Second, we intend to evaluate the effects of other confounding variables such as autoimmune diseases, which increase the likelihood of information bias. Despite these limitations, this meta-analysis can provide strong evidence of a significant association between aspirin and NHL. Since senility analyses, limiting the inclusion of studies according to the data of publication or the size of the study, produce results nearly identical to the primary result.

In addition, 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.

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