Red Meat Intake and Risk of Non-Hodgkin Lymphoma: A Meta-Analysis

Hosein Fallahzadeh¹, Maria Cheraghi², Neda Amoori³*, Mehrangiz Alaf⁴

Abstract

Background: While the incidence of non-Hodgkin lymphoma (NHL) has been rising worldwide, the reasons remain undefined. Recent research has focused on effect of red and processed meat intake as a risk factor, but with inconclusive results. We therefore conducted a meta-analysis of data published to date, to ascertain the overall association between intake and NHL. Materials and Methods: A published literature search was performed through PubMed, Cochrane Library, Medline, and Science Citation Index Expanded databases for articles published in English. Pooled odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated using random or fixed effects models. Heterogeneity was assessed using Chi-square and I² statistics. Dissemination bias was evaluated by funnel plot analysis. We performed a formal meta-analysis using summary measures from these studies. Results: In total, 11 published studies were included in the final analysis. The combined analysis revealed that there was significant association between the red meat and NHL risk (OR=1.10, 95%CI: 1.02 to 1.19, p=0.01). Additionally, there was showed significance association between processed red meat and NHL risk (OR=1.17, 95%CI: 1.06 to 1.29, p=0.001). In subgroup analysis, a statistical significant association was noted between diffuse large B-cell lymphoma (DLBCL) (OR=1.20, 95%CI: 1.04 to 2.37, P=0.01) and red meat intake. Conclusions: In this meta-analysis, there was evidence for association between consumption of red meat, or processed meat and risk of NHL, particularly with the DLBCL subtype in the red meat case.

Keywords: Red meat - non-Hodgkin lymphoma - risk factor - meta-analysis

RESEARCH ARTICLE

Red Meat Intake and Risk of Non-Hodgkin Lymphoma: A Meta-Analysis

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Introduction

Non-Hodgkin lymphoma (NHL), a heterogeneous group of malignancies of the lymphoid tissue, is the seventh most common cancer in U.S. men and women with more than half of cases occurred in adults aged 65 y (Kabat et al., 2012; Zekri et al., 2013; Binesh et al., 2014). Caucasian have a 50% higher incidence rate than African-Americans and Asians and a 15% lower risk than Latinos (Parkin et al., 2003; Amoori et al., 2014). There is also evidence that the NHL incidence rate is almost twice as high among American-Asians compare to Asians living in their country of origin (Kabat et al., 2012). The most established risk factor for NHL is immunosuppression due to primary immune disorders or acquired immune deficiencies (Yildirim et al., 2013; Karimi et al., 2014). However, these causes of severe immunodeficiency are relatively rare.

Growing evidence suggests that common lifestyle factors and environmental risk factors with modest increases in risk in conjunction with host genetic susceptibility are more critical contributors to lymphoma risk in the general population (Zhang et al., 2011; Chiu et al., 2003; Yildirim et al., 2013). Some prospective studies have linked intake of red meat, processed meat to increased NHL risk (Chiu et al., 2003; Evens et al., 2008), but the evidence is limited and inconsistent, particulary among histologic subtypes of NHL (Sangrajrang et al., 2011; Amanat et al., 2013; Karami et al., 2014). However, there are not a stable relation between red meat, processed meat and NHL, and positive, negative, and null relations have been reported. We carry out an updated meta-analysis study to determine the overall association between intake red meat, processed meat and the NHL.

Materials and Methods

Literature and search strategy

We searched Pub Med, Cochrane Library, Medline, and Science Citation Index Expanded databases for case-control and cohort studies on intake red meat, processed meat and the NHL in English. The following search terms
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were used: (Non-hodgkins lymphoma, NHL, Processed meat, Follicular lymphoma, FL, Diffuse large Bcell, DLBCL, Chronic lymphocytic leukemia, CLL/SLL. In addition, reference lists were also reviewed manually. The latest search was performed on September 5, 2014.

Inclusion and exclusion criteria

In order for articles to be included in our study, the following criteria must be met: i) case-control or cohort studies; ii) evaluating the relationship between intake red meat, processed meat and the NHL; iii) 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: i) repeated reports; ii) 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 (Neda Amoori and Hosein Falahzadeh) and disagreements were solved by a third researcher (Maria Cheraghi). For each eligible study, the following characteristics were collected: first author, year of publication, study design, Area, 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 evaluate qualitatively heterogeneous data, the chi-square test was used in confidence level of 10% (p<0.1). The test “$I^2$ (1)” 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 Hansel, 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 11 published articles regarding the relationship between intake red meat, processed meat...
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Red Meat Intake and Risk of Non-Hodgkin’s Lymphoma (NHL) has been a topic of interest in cancer research. Several studies have investigated the association between red meat consumption and NHL risk, but the results have been mixed. A meta-analysis was conducted to synthesize the available evidence from existing case-control and cohort studies.

### Study Characteristics

The main characteristics of the 11 studies included in the meta-analysis are summarized in the table below. Of these studies, 7 were population-based case-control studies and 4 were cohort studies. The studies were published between 2003 and 2013 and involved a total of 11,432 cases and 16,073 controls. More details of these studies were summarized in Supplementary Table 1.

### The Results of Meta-analysis

Using the random-effect model, meta-analysis showed a significant association between red meat and NHL risk (OR=1.10, 95% CI: 1.02 to 1.19, p=0.01), the forest plot was shown in Figure 2. The publication bias among studies of red meat intake and NHL was not appreciable based on funnel plots (Figure 3).

Processed red meat and NHL risk meta-analysis for processed red meat showed significant association between processed red meat and NHL risk (OR=1.17, 95% CI: 1.06 to 1.29, p=0.001), under the random-effect model the forest plot was shown in Figure 4.

Analysis using the available data of red meat also revealed no statistical significant association between:(a) lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) (OR=1.12, 95% CI: 0.47 to 1.67, p=0.58); (b) Follicular lymphoma (FL) (OR=1.11, 95% CI: 0.93 to 1.15, p=0.24) and showed statistical significant association between Diffuse large B-cell lymphoma (DLBCL) (OR=1.20, 95% CI: 1.04 to 2.37, p=0.01)(Figure 5).

### Discussion

In this meta-Analysis, there was strong evidence indicated that consumption red meat and processed meat is a risk factor for progression of NHL. There was strong statistical association was seen between red meat intake and the risk of Diffuse large B-cell (DLBCL) in different subtypes.

In case control study suggested by Kilfoy et al found that the risk of NHL total was associated...
with a higher intake of red meat NHL sub group analyses showed that DLBCL was associated with intake of red meat but not any of the macronutrients or doneness groups evaluated. Follicular lymphoma was associated with a higher intake of total fat and oleic acid, but not any of the meat groups evaluated. The power to evaluate the association for CLL/SLL or for T cell lymphoma histologic types was limited. An excess risk of NHL has been reported with higher intake of meat (Purdue et al., 2004), red meat (Chiu et al., 1996; Zhang et al., 1999; Purdue et al., 2004; Kilfoy et al., 2012; Stefani et al., 2013), and processed meat (Purdue et al., 2004), whereas other studies found no association with meat consumption (Cross et al., 2006; Talamini et al., 2006; Chang et al., 2006; Erber et al., 2009; Rohrmann et al., 2011; Daniel et al., 2012).

In this Meta analysis study, we identified an association for NHL with higher intake of red meat and processed meat. The increased risk for NHL associated with high meat intake has been hypothesized to be due to the effects of fat and protein (Zhang et al., 1999). Consistent with two cohort studies, observed a positive association with the intake of total fat and oleic acid (a type of monounsaturated fat) is consistent with the report of one cohort study (Chiu et al., 1996), but not others that have reported an inverse (Zhang et al., 1999; Polesel et al., 2006) or no association (Purdue et al., 2004; Chang et al., 2006) .Components of both innate and acquired immunity, including the production of key inflammatory cytokines, can be affect by fatty acids (Calder et al., 2002). There is considerable evidence that the immune system is sensitive to both the quantity of dietary fat and the degree of saturation (Davis et al., 1992). Monounsaturated fatty acids and the n-6 polyunsaturated fatty acids are believed to decrease immune function through suppression of lymphocyte proliferation and inhibition of production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) (Purdue et al., 2004; Stefani et al., 2013), whereas the n-3 polyunsaturated fatty acids promote immune function and are well known for their anti-inflammatory properties (Yaqoob et al., 2002; Amoori et al., 2014). However, the effects of specific types of fat on immune function in humans and the subsequent development of NHL are not well understood.

Meat comprises both fat and protein and is also a source of mutagenic compounds, such as N-nitroso compounds formed during the preservation process as well as heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) formed during cooked. A previous case-control study (Stefani et al., 2013) and cohort study (Chiu et al., 1996) found an increased risk for NHL

Table 2. Subgroup Analysis of Meat (Red Meat, Processed Meat) and NHL Risk

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No. of studies</th>
<th>Odds ratio 95%CI</th>
<th>P</th>
<th>Model</th>
<th>Heterogeneity I²(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red meat</td>
<td>11</td>
<td>1.10(1.02-1.19)</td>
<td>0.01</td>
<td>Random</td>
<td>59.4 0.001</td>
</tr>
<tr>
<td>Processed meat</td>
<td>8</td>
<td>1.17(1.06-1.29)</td>
<td>0.001</td>
<td>Random</td>
<td>45.3 0.04</td>
</tr>
</tbody>
</table>

Table 3. Analysis of Red Meat and Subgroup NHL Risk

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No. of studies</th>
<th>Odds ratio 95%CI</th>
<th>P</th>
<th>Model</th>
<th>Heterogeneity I²(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLL/SLL</td>
<td>5</td>
<td>1.12(0.74-1.67)</td>
<td>0.58</td>
<td>Random</td>
<td>93.4 0.01</td>
</tr>
<tr>
<td>FL</td>
<td>5</td>
<td>1.11(0.93-1.32)</td>
<td>0.24</td>
<td>Random</td>
<td>76.7 0.001</td>
</tr>
<tr>
<td>DLBCL</td>
<td>5</td>
<td>1.26(1.04-1.54)</td>
<td>0.01</td>
<td>Random</td>
<td>74.9 0.001</td>
</tr>
</tbody>
</table>
in the highest tertile of red meat consumption, the cohort study identified that the main component contributing to this risk was hamburgers (Purdue et al., 2004). The degree to which meat is cooked has previously been associated with NHL; women in Iowa who cooked their meat well-done has a significantly lower risk of NHL compared with those who preferred their meat cooked medium- rare or rare (Chiu et al., 1996).

In this meta-analysis, there were a number of limitations and potential bias. First, it seemed that 2 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 intake red meat, processed meat and the NHL. Since sensitivity analyses, limiting the inclusion of studies according to the data of publication or the size of the study, produces results nearly identical to the primary result.

In addition, new information was obtained about the relation between intake red meat, processed meat and the NHL, as follows: a) Obtaining a summary of data on estimating odds ratio to the effect of intake red meat, processed meat on NHL. b) Significant direct correlation between the effect of intake red meat, processed meat and incidence NHL. c) Significant direct correlation between the effects of intake red meat and incidence DLBCL. d) Identifying the impact of different variables on the relation between intake red meat, processed meat and the NHL such studies design, quality of studies.

References


