RESEARCH ARTICLE

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

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Abstract

Background: While the incidence of non-Hodgkins lymphoma (NHL) has been rising worldwide, the reasons remain undefined. Recent research has focused on effect of red andf 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-Hodgkins lymphoma - risk factor - meta-analysis

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Introduction

Non-Hodgkins 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 immunosuppress due to primary immune disorders or acquired immune deficiencies (Yildirim et al., 2013; Karami 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.

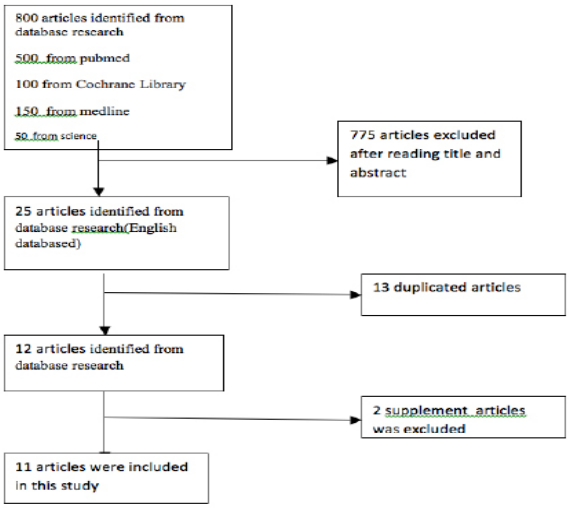

Figure 1. Flow Chart of Study Selection

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

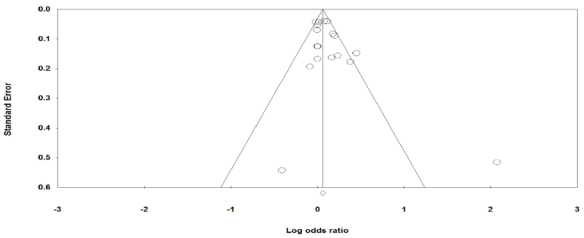

Figure 3. Funnel Plot of Studies of NHL Risk after Red Meat Intake

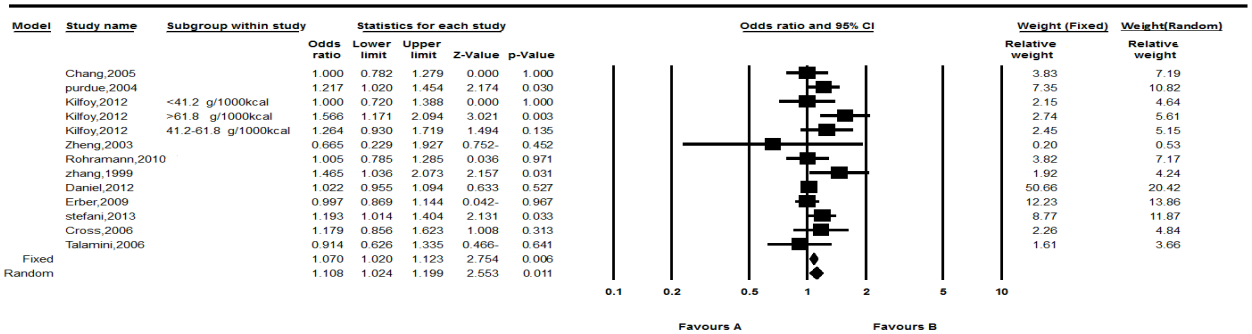

Figure 2. Forest Plot of Odds Ratio Estimates of NHL for Persons who Intake Red Meat

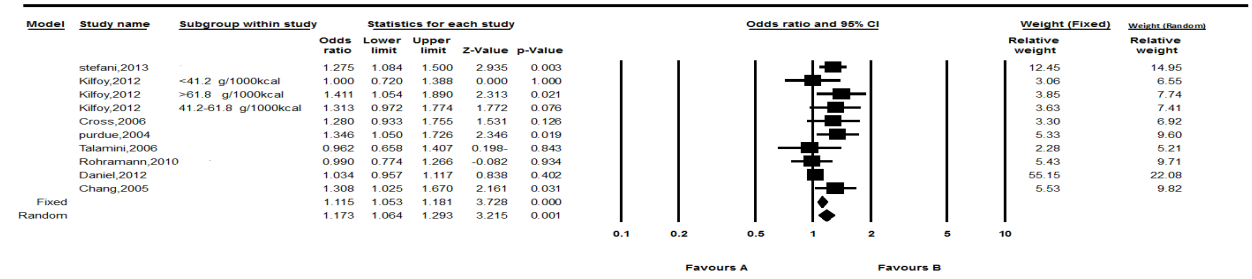

Figure 4. Forest Plot of Odds Ratio Estimates of NHL for Persons who Intake Processed Red Meat

Table 1. Characteristics of the Studies Correlating with the Effects Red Meat on NHL Risks

NO	Study(ref.)	Area	Source of case	Source of controls	Ascertainment measure	Adjustment factor
1	Chang et al., 2005	Scandinavian	Case identified from6 regional cancer registries &rapid reporting system	Pop controls sampled by random digit dialing and from medicare files	Questionnaire & tel.interview	Age &sex
2	Kilfoy et al., 2012	Nebraska	Case residing in66 countries in eastern nebraska identified by rapid case finding system	Pop controls sampled by random digit dialing and from medicare files	questionnaire (HHHQ+FFQ)	Age &sex
3	Zhang et al., 2003	Connecticut	Cases identified through the yale comprehensive cancer centers rapid case finding &tummor registry	Pop controls sampled by random digit dialing and it was for health care financing administration controls	self report	Age, bmi, family history
4	Rohrmann et al., 2010	European Countrieas	Cohort prospective in 23centers in 10 european countries	Hospital based epidemiologic research program at EPIC european prospective investigation into cancer and	questionnaire (FFQ)	Age, bmi, physical activity, alchol drinking
5	Daniel et al., 2012	USA	Cancer cases were ascertained through linkage with the 8 original state cancer registries plus	Nutrition pop controls sampled by random digit dialing and it was for health care financing administration controls	self report	BMI, exercise, smoking, family history
6	Erber et al., 2009	Hawaii	Hawaii tumor Registry, cancer survilance program state of california cancer, registry and death certificates and national death inndex	Pop controls sampled by random digit dialing and from medicare files	questionnaire (QFFQ)	Age, ethnicity education, alchol intake& age at first live birth
7	Talamini et al., 2006	Italian	Case ascertainment from the major hospitals under survilance in north eastern italy	Hospital controls admitted for acute conditions (e.g, malignant, chronic bronchitis, cardiovascular illness	FFQ questionnaire	BMI, age, smoking, family history
8	Cross et al., 2006	USA	Incidence case from four SEER regions Identified by rapid reporting system	Pop controls sampled from the four SEER regions by random digit dialing and from medicare/medical files	questionnaire (FFQ)	Age, Race, gender, study center
9	Stefani, 2013	USA	Case identified from National Cancer Institute of Montevideo and Uruguay	Pop controls sampled by random digit dialing and from medicare files	Interviews and Questionnaire	Age, sex, residence, education, income
10	Zheng, 2003	Connecticut	Case identified from Connecticut Tumor Registry	Pop controls sampled by random digit dialing and from medicare files	Interviews	Age
11	Purdue, 2004	Canada	Case identified from canada Tumor Registry	Pop controls sampled by random digit dialing and from medicare files	Questionnaire	Age &sex

and the NHL were identified by applying the inclusion criteria (Figure 1) (Zhang et al., 1999; Purdue et al., 2004; Chang et al., 2005; Cross et al., 2006; Talamini et al., 2006; Erber et al., 2009; Rohramann et al., 2010; Daniel et al., 2012; Kilfoy et al., 2012; Stefani et al., 2013) 8 articles documented processed meat (Purdue et al., 2004; Cross et al., 2006; Talamini et al., 2006; Rohramann et al., 2010; Daniel et al., 2012; Kilfoy et al., 2012; Stefani et al., 2013) and 5 articles reported intake red meat and risk subtype NHL (Purdue et al., 2004; Chang et al., 2005; Erber et al., 2009; Daniel et al., 2012; Kilfoy et al., 2012).

Study characteristics

The main characteristics of the 11 studies are as follows, of which 7were population-based case-control studies and4 were cohort study. Eleven studies were published between 2003 and 2013 and involved 11432 cases and 16073 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 significant association between the 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 risk was not appreciable based on funnel plots (Figure 3).

Processed red meat and NHL risk meta-analysis for processed red meat showed significance 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)(Figure5). The results were shown in Tables 2 and Table 3.

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 Bcell(DLBCL) in different subtypes.

In case control study suggested by Kilfoy et al found that the risk of NHL total was associated

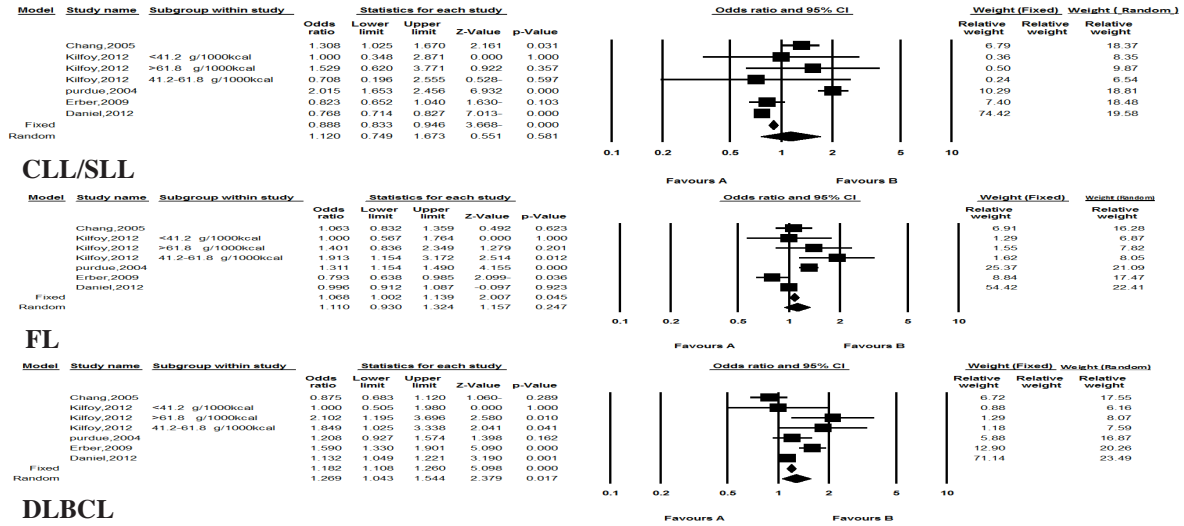

Figure 5. Risk Estimates of the Odds Ratio of Developing NHL for Persons Who Intake Meat, by Lymphoma Subtype. FL indicates follicular lymphoma. DLBCL, Diffuse large B-cell lymphoma and CLL/SLL, chronic lymphocytic leukemia/ small lymphocytic lymphoma

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

Subgroups	No. of studies	Odds ratio		Model	Heterogeneity	
		95%CI	P		I^2(%)	P
Red meat	11	1.10(1.02-1.19)	0.01	Random	59.4	0.001
Processed meat	8	1.17(1.06-1.29)	0.001	Random	45.3	0.04

Table 3. Analysis of Red Meat and Subgroup NHL Risk

Subgroups NHL	No. of studies	Odds ratio		Model	Heterogeneity	
		95%CI	P		I^2 (%)	P
CLL/SLL	5	1.12(0.74-1.67)	0.58	Random	93.4	0.01
FL	5	1.11(0.93-1.32)	0.24	Random	76.7	0.001
DLBCL	5	1.26(1.04-1.54)	0.01	Random	74.9	0.001

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.the finding of a borderline increased risk from 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

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 sensivity 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

Amanat A, Al-Belushi B, Waly M, Al-Moundhri M, Burney Ik (2013). Dietary and lifestyle factors and risk of non-Hodgkin's lymphoma in Oman. *Asian Pac J Cancer Prev*, **14**, 841-8.

Amoori N, Mirzaei M, Cheraghi M(2014). Incidence of cancers in kuzestan province of Iran: Trend from 2004 to 2008. *Asian Pac J Cancer Prev*, **15**, 8345-9.

Binesh F, Akhavan A, Behniafard N, Atefi A(2014). Clinicopathologic and survival characteristics of childhood and adolescent non-Hodgkin's lymphoma in Yazd, Iran. *Asian Pac J Cancer Prev*, **15**, 1585-8.

Calder PC, Grimble RF (2002). Polyunsaturated fatty acids, inflammation and immunity. *Eur J Clin Nutr*, **56**, 14-9

Chang ET, Balter KM, Torrang A, et al (2006). Nutrient intake and risk of non-Hodgkin's lymphoma. *Am J Epidemiol*, **164**, 1222-32.

Chiu BC, Cerhan JR, Folsom AR, et al (1996). Diet and risk of non-Hodgkin lymphoma in older women. *JAMA*, **275**, 1315-21.

Cross AJ, Ward MH, Schenk M, et al (2006). Meat and meat-mutagen intake and risk of non-Hodgkin lymphoma: results from a NCI-SEER case-control study. *Carcinogenesis*, **27**, 293-7.

Daniel CR, Sinha R, Park Y, et al (2012). Meat intake is not associated with risk of non-hodgkin lymphoma in a large prospective cohort of US men and women. *J Nutrition*, **142**, 1074-80.

Davis S (1992). Nutritional factors and the development of non-Hodgkin's lymphoma: a review of the evidence. *Cancer Res*, **52**, 5492-5.

Erber E, Maskarinec G, Gill JK, Park S-Y, Kolonel LN (2009). Dietary patterns and the risk of non-Hodgkin lymphoma: the Multiethnic Cohort. *Leukemia Lymphoma*, **50**, 1269-75.

Kabat GC, Kim MY, Wactawski-Wende J, et al (2012). Anthropometric factors, physical activity and risk of Non-hodgkin's lymphoma in the women's health initiative. *Cancer Epidemiology*, **36**, 52-9.

Karami K, Cheraghi M, Amori N, Pedram M, Sobhani A(2014). Common Cancers in Khuzestan Province, South West of Iran, during 2005-2011. *Asian Pac J Cancer Prev: APJCP*, **15**, 9475-8

Kilfoy B, Nicholas J, Kolar Ca, et al (2012). Meat intake and risk of non-Hodgkin lymphoma. *Cancer Causes Control*, **23**, 1681-92.

Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (2003). Cancer Incidence in Five Continents.

Polesel J, Talamini R, Montella M et al (2006). Linoleic acid,vitamin D and other nutrient intakes in the risk of non-Hodgkin lymphoma: an Italian case-control study. *Ann Oncol*, **17**, 713-8.

Purdue MP, Bassani DG, Klar NS, Sloan M, Kreiger N(2004). Dietary factors and risk of non-Hodgkin lymphoma by histologic subtype: a case-control analysis. *Cancer Epidemiol Biomarkers Prev*, **13**, 1665-76.

Rohrmann S, Linseisen J, Jakobsen MU, et al(2011). Consumption of meat and dairy and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*, **128**, 623-34.

Salim EI, Jazieh AR, Moore MA (2011). Lung cancer incidence in the Arab league countries; risk factors and control. *Asian Pac J Cancer Prev*, **12**, 17-34.

Sangrajrang S, Renard H, Kuhaprema T, et al (2011). Personal use of hair dyes - increased risk of non-Hodgkin's lymphoma in Thailand. *Asian Pac J Cancer Prev*, **12**, 2393-6.

Stefani E, Ronco AL, Deneo-Pellegrini H, et al (2013). Meat, milk and risk of lymphoid malignancies: a case-control study in Uruguay. *Nutrition Cancer*, **65**, 375-83

Talamini R, Polesel J, Montella M, Dal Maso L, Crovatto M, Crispo A, et al (2006). Food groups and risk of non Hodgkin lymphoma: A multicenter, case control study in Italy. *Int J Cancer*, **118**, 2871-6.

Yaqoob P (2002). Monounsaturated fatty acids and immune function. *Eur J Clin Nutr*, **56**, 9-13.

Yildirim M, Karakilinc H, Yildiz M, et al (2013). Non-hodgkin lymphoma and pesticide exposure in Turkey. *Asian Pacific J Cancer Prev*, **14**, 3461-3.

Zekri AR, Hassan ZK, Bahnassy AA et al (2013). Gene expression profiling of non-Hodgkin lymphomas. *Asian Pac J Cancer Prev*, **14**, 4393-8.

Zhang S, Hunter DJ, Rosner BA, et al (1999). Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. *J National Cancer Institute*, **91**, 1751-8.

Zheng T, Holford TR, Leaderer B, et al (2004). Diet and nutrient intakes and risk of non-Hodgkin's lymphoma in Connecticut women. *Am J Epidemiol*, **159**, 454-66.