Red and Processed Meat Consumption Increases Risk for Non-Hodgkin Lymphoma

A PRISMA-Compliant Meta-Analysis of Observational Studies

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Abstract: The association between consumption of red and processed meat and non-Hodgkin lymphoma (NHL) remains unclear. We performed a meta-analysis of the published observational studies to explore this relationship.

We searched databases in MEDLINE and EMBASE to identify observational studies which evaluated the association between consumption of red and processed meat and risk of NHL. Quality of included studies was evaluated using Newcastle-Ottawa Quality Assessment Scale (NOS). Random-effects models were used to calculate summary relative risk (SRR) and the corresponding 95% confidence interval (CI).

We identified a total of 16 case–control and 4 prospective cohort studies, including 15,189 subjects with NHL. The SRR of NHL comparing the highest and lowest categories were 1.32 (95% CI: 1.12–1.55) for red meat and 1.17 (95% CI: 1.07–1.29) for processed meat intake. Stratified analysis indicated that a statistically significant risk association between consumption of red and processed meat and NHL risk was observed in case–control studies, but not in cohort studies. The SRR was 1.11 (95% CI: 1.04–1.18) for per 100 g/day increment in red meat intake and 1.28 (95% CI: 1.08–1.53) for per 50 g/day increment in processed meat intake. There was evidence of a nonlinear association for intake of processed meat, but not for intake of red meat.

Findings from our meta-analysis indicate that consumption of red and processed meat may be related to NHL risk. More prospective epidemiological studies that control for important confounders and focus on the NHL risk related with different levels of meat consumption are required to clarify this association.

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Abbreviations: BMI = body mass index, DLBCL = diffuse large B-cell lymphoma, FFQs = food frequency questionnaires, FL = follicular lymphoma, GLST = generalized least-squares trend estimation, HCAs = heterocyclic amines, NHL = non-Hodgkin lymphoma, NOCs = *N*-nitroso compounds, NOS = Newcastle-Ottawa Scale, PAHs = polycyclic aromatic hydrocarbons, SLL/CLL = small lymphocytic lymphoma/chronic lymphocytic leukemia, SRR = summary relative risk.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies arising from lymphoid tissue. Established risk factors, such as immunodeficiency and viral infection, are only responsible for a small proportion of cases.[1] In addition to these, it is thought that certain medical conditions[2] and lifestyle factors, including obesity[3] and tobacco smoking,[4] may be implicated. Although the evidence is both inconsistent and limited, it has been suggested that dietary factors may also play a role in the development of NHL.[5,6]

Consumption of red and processed meat has long been known to be associated with an increased risk of various cancers, such as of the colorectum, esophagus (squamous cell carcinoma), liver, lung, and prostate.[7] Heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), formed during cooking of meat at high temperatures, are well-established carcinogens.[8–10] In addition, *N*-nitroso compounds (NOCs), which are formed in processed meat containing high levels of nitrates and nitrites, are also implicated in the development of various human tumors.

Many epidemiological studies have investigated the association between the consumption of red and processed meat and the risk of NHL, with mixed results.[11–30] Based on a meta-analysis of the data from 3 cohort and 8 case–control studies, Fallahzadeh and colleagues concluded that high consumption levels of red and processed meat may increase the risk of NHL. However, there was significant heterogeneity between studies ($P < 0.01$).[6] Unfortunately, they failed to include several relevant studies,[11,12,14,15,21–23,27,28] and did not explore the source of the heterogeneity. In addition, the dose–response relationship between the consumption of red and processed meat and the risk of NHL has not been clearly defined. In order to better understand this, we carried out a comprehensive meta-analysis of observational studies, using our own methods and criteria for the selection of studies, in the presentation of the

data, in the interpretation of the evidence, and in the conclusions drawn.

METHODS

We performed a meta-analysis of the association between the consumption of red and processed meat and the risk of NHL, following the PRISMA criteria.[31] Given that the data used had all been published previously, ethics committee approval was not required. The searches, selection of studies for inclusion, data extraction, and the quality assessments were performed independently by 2 of the authors (YL and DJM); disagreements were resolved by discussion.

Data Sources and Searches

Studies published in English up to the end of January 2015 were eligible for inclusion. We performed MEDLINE and EMBASE searches using the following key words and strategies: cancer or lymphoma; and red meat or processed meat or preserved meat or beef or pork or veal or mutton or lamb or ham or sausage or bacon; and risk or incidence or prevalence. Potentially relevant papers were retrieved and assessed. The references in the articles were checked to identify additional publications of interest.

Study Selection

The definitions of red and processed meat varied across studies. For the purposes of the study we defined red meat as beef, veal, pork and lamb, or any combination thereof. We defined processed meat as products made from pork, beef, or lamb that had been preserved by curing, smoking, frying, or drying.[13] Studies of the association between red and processed meat consumption and the risk of NHL were eligible for inclusion if they were observational (cohort or case–control), undertaken in humans, and reported relative risk (RR) estimates (hazard ratios, risk ratios, or odds ratios) with corresponding 95% confidence intervals (CIs). We excluded experimental and mechanistic studies, nonpeer reviewed articles, ecologic assessments, and correlation studies. We also excluded studies published only as abstracts or commentaries. When multiple reports were available on the same study, only the most informative one was considered.

Data Extraction

Information on study design, location, publication year, number of subjects (cases, controls, or cohort size), type of controls, duration of follow-up for cohort studies, dietary assessments, comparison groups, methods of outcome assessment, RR estimates and the corresponding CIs for the highest versus lowest intake level, and adjustment variables was extracted. The RRs were determined using the most adjusted multivariate model. For the purposes of the analysis, one study, which reported results according to t(14;18) status,[21] was considered by us as being 2 separate ones. Another study analyzed their data according to the method used for meat processing.[18] We extracted from it the findings pertaining to fried red meant, as this accounted for most of the processed meat consumed.

Quality Assessment of Individual Studies

A quality assessment of included studies was undertaken using the Newcastle-Ottawa Scale (NOS).[32] This instrument assesses the quality of case–control and cohort studies against three parameter: selection (4 items, with each being awarded 1 star), comparability (1 item, which can be awarded up to 2 stars), and exposure/outcome (3 items, with each being awarded 1 star). A score of ≥7 stars is indicative of a high quality study. Studies for which there was insufficient information available for NOS scoring were considered to be of low quality.

Statistical Methods

We calculated summary relative risk (SRR) and 95% CI to measure the impact of the highest versus the lowest level of red and processed meat consumption on the risk of NHL using a random effect model, according to the method described by DerSimonian and Laird,[33] which takes into account both within and between study heterogeneity. When sex-specific estimates were available, we analyzed for this separately.

To evaluate the between-study heterogeneity of included studies, we used the χ^2 test, defining significant heterogeneity as a P-value < 0.10, and assessed inconsistency using the I^2 statistic. An I^2 value of over 50% indicates that high between-study heterogeneity may be present. An I^2 value of under 25% indicates no significant heterogeneity.[34] We carried out strata and linear meta-regression analysis based on geographic locations, study design (case–control vs. cohort study), type of food frequency questionnaires (FFQs, validated vs. not validated), study quality score, number of cases, and confounders (smoking status, body mass index [BMI], alcohol use, dietary energy intake, and vegetable and fruit intake). We also examined the associations for subtypes of NHL (diffuse large B-cell lymphoma [DLBCL], follicular lymphoma [FL], small lymphocytic lymphoma/chronic lymphocytic leukemia [SLL/CLL], and T-cell lymphoma). Sensitivity analyses were conducted by omitting one study at a time and examining the influence of each individual study on the overall RR.

When possible, linear dose–response analysis was carried out per increment in consumption of 100 g of red meat and 50 g of processed meat daily using generalized least-squares trend estimation (GLST) analysis, as developed by Greenland and Orsini.[35,36] This method requires medians for ≥3 category levels of consumption. When medians were not available, we calculated the midpoint of the upper and lower boundaries in each category as the average intake level. When the lowest category was open ended, the lowest boundary was considered as zero. When the highest category was open ended, the open-ended boundary was calculated using an interval length of the width of the closest interval. When exposure was reported as frequency of consumption, as in the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) report,[37] we transformed the quantitative exposure units into grams per day by assuming that a standard ''serving'' or ''portion'' corresponded to 120 g for red meat and 50 g for processed meat. For studies reporting intakes in grams/1000 kcal/day,[25,26,30] the intake in grams/day was estimated using the average energy intake reported in the relevant article. We carried out a potential nonlinear dose–response analysis using the best-fitting 2-term fractional polynomial regression model.[38] A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity.[38]

To evaluate publication bias, we used the contour enhanced funnel plot and the Egger regression test.[39] All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX) and R-package (Version 2.11.0 beta, R
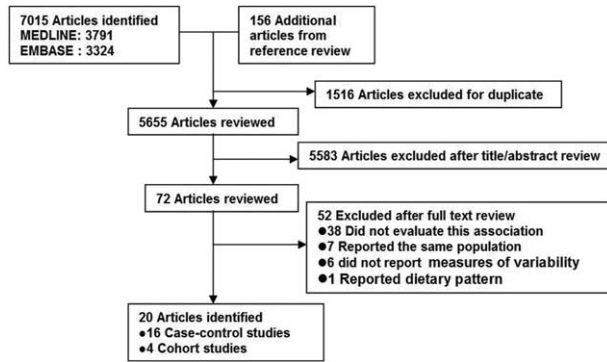
FIGURE 1. Flow diagram of the systematic literature search on red and processed meat intake and the risk of non-Hodgkin lymphoma.

Development Core Team, Auckland, NJ) statistical software. A 2-tailed *P*-value of <0.05 represented significance.

RESULTS

Search Results and Study Characteristics

The search strategy generated 7015 citations (Fig. 1). From the reference review, we included an additional 156 articles. On the basis of the titles and abstracts, we identified 72 potentially relevant articles. Of these, 39 were subsequently assessed as being nonrelevant, 6 were excluded because they did not report the odds ratio (OR) or RR and the corresponding 95% CI, or sufficient information to calculate them. One was excluded because it reported for the association between dietary pattern and NHL risk. Seven articles were excluded on the basis that they represented multiple reports of the same study. This left 20 eligible studies, published between 1996 and 2013. They comprised 4 prospective cohort studies,[11,13,24,26] and 9 population-based[16–18,21–23,25,30,40] and 7 hospital-based case–control studies[12,14,15,20,27–29] (Table 1). A total of 15,189 subjects with NHL were included. Eleven studies were from the North America, 5 from Europe, 2 from Asia, and 2 from Uruguay. All used FFQs for the assessment of meat consumption. Most considered or adjusted for the effects of smoking, alcohol consumption, BMI, and total energy intake. The NOS scores ranged from 6 to 9; seventeen studies were deemed to be of a high quality (≥7 stars) (Suppl. Table 1, http://links.lww.com/MD/A508).

Red Meat

High Versus Low intake analysis

The summary RR of NHL for the highest group compared with the lowest group of red meat intake was 1.32 (95% CI, 1.12–1.55). There was evidence of strong between study heterogeneity across these studies ($P_{\text{heterogeneity}} < 0.001$, $I^2 = 79.0\%$, Fig. 2A).

Dose–Response Analysis

Thirteen studies could be used in the dose–response meta-analysis. The SRR of NHL was 1.11 (95% CI, 1.04–1.18) per 100 g/day of red meat, with evidence of moderate between study heterogeneity ($P_{\text{heterogeneity}} = 0.067$, $I^2 = 39.0\%$, Fig. 2B). There was no evidence of a nonlinear association of red meat intake and NHL risk ($P = 0.351$, Fig. 2C).

Processed Meat

High Versus Low Intake Analysis

The SRR of NHL for the highest group compared to the lowest group of processed meat intake was 1.17 (95% CI, 1.07–1.29). There was evidence of moderate between study heterogeneity ($P_{\text{heterogeneity}} = 0.057$, $I^2 = 37.1\%$, Fig. 3A).

Dose–Response Analysis

Fourteen studies could be used in the dose–response meta-analysis. The SRR of NHL was 1.28 (95% CI, 1.08–1.53; $P_{\text{heterogeneity}} < 0.001$; $I^2 = 72.4\%$; Figure 3B) per 50 g/day of processed meat. There was evidence of a nonlinear association of processed meat intake and NHL risk ($P = 0.031$, Figure 3C).

Publication Bias

Egger test did not reveal evidence of publication bias for either red meat ($P = 0.567$, Suppl. Figure 1A, http://links.lww.com/MD/A508) and processed meat consumption ($P = 0.181$, Suppl. Figure 1B, http://links.lww.com/MD/A508).

Subgroup, Meta-Regression and Sensitivity Analyses

The results of stratified and meta-regression analyses are shown in Table 2. For red meat consumption, we observed an increased risk of NHL in case–control studies (SRR = 1.34; 95% CI, 1.09–1.65), but not in cohort studies (SRR = 1.17; 95% CI, 0.92–1.49). The pooled RR was 2.12 (95% CI, 0.80–5.59; n = 3 studies) for men and 1.61 (95% CI, 1.06–2.45; n = 4 studies) for women. There was significant between-subgroup heterogeneity between studies which used different FFQs (validated vs. not validated, *P* for difference = 0.09), were of different quality (high vs. low, *P* for difference = 0.087), and followed adjustments for vegetable and fruits intake (*P* for difference = 0.051). This partly explained the overall high heterogeneity.

For processed meat consumption, we found an increased risk of NHL in case–control studies (SRR = 1.21; 95% CI, 1.07–1.36), but not in cohort studies (SRR = 1.07; 95% CI, 0.97–1.19). There was significant between-subgroup heterogeneity between studies when adjusted for BMI (*P* for difference = 0.018). This partly explained the overall high heterogeneity.

The estimation of overall homogeneity and the effect of removing one study at a time from the analysis confirmed the stability of the relationship between red and processed meat intake and NHL risk (data not shown). In addition, repeat analysis of high versus low intake using the studies included in the linear dose–response analysis yielded results similar to those of the original analysis (red meat: SRR = 1.20; 95% CI, 1.07–1.35; $P_{\text{heterogeneity}} = 0.045$; $I^2 = 42.8\%$ and processed meat: SRR = 1.17; 1.17; 95% CI, 1.05–1.30; $P_{\text{heterogeneity}} = 0.029$; $I^2 = 44.3\%$).

NHL Subtypes

Six studies[18,24–26,28,30] gave risk estimates for the association between red and processed meat consumption and NHL subtypes. We found a significant association between processed meat consumption and DLBCL risk (SRR = 1.23; 95% CI, 1.03–1.48), but no other significant associations (Fig. 4A and B).

Individual Meat Items

Intake of salted meat and fried meat were positively associated with NHL risk (salted meat: SRR = 2.34; 95% CI,

TABLE 1. Characteristics of Studies of Red and Processed Meat Consumption and Non-Hodgkin Lymphoma Risk

Author/Year/Country	Study Characteristics	Type of Questionnaire	Case Ascertainment	Exposure Details (Highest vs. Lowest)	RR (95% CI) (Highest vs. Lowest)	Adjustments
Case–control						
De Stefani/1998/Uruguay[12]	H-B, 160 NHL, 163 controls	Self-administered questionnaire, NA	Histological	Red meat: >12.7 vs. <7.7 servings/week Red meat: >9.3 vs. <6.0 servings/week Processed meat: >1.1 vs. <0.2 servings/week Processed meat: >1.1 vs. <0.2 servings/week	2.53 (1.01–6.34) M, 2.45 (0.88–6.82) F, 1.03 (0.43–2.42) M, 1.90 (0.66–5.45) F	Age, residence, urban/rural status, type of tobacco, beer intake, mate
Tavani/2000/Italy[14]	H-B, 200 NHL, 7990 controls	Self-administered questionnaire, NA	Histological	Red meat: >6 vs. <3.0 servings/week	1.2 (0.8–1.7)	Age, year of recruitment, sex, education, smoking, alcohol, fat, fruit and vegetable intakes
Matsuo/2001/Japan[15]	H-B, 333 NHL, 55,904 controls	Self-administered questionnaire, NA	Histological	Beef: high vs. low	0.99 (0.69–1.43)	Age, sex
Zheng/2004/USA[17]	P-B, 601 NHL, 717 controls	Interviewer FFQ-120 validated	Histological	Bacon: >3 vs. <1 servings/month	0.7 (0.5–1.0)	Age, BMI, family history of NHL, total energy intake
Purdue/2004/Canadia[16]	P-B, 1642 NHL, 5039 controls	Self-completed FFQ-60, validated	Histological	Red meat: >4 vs. <1.9 servings/week, processed meat >4 vs. <1.3 servings/week	1.11 (0.93–1.33), 1.49 (1.24–1.80)	Age, sex, income adequacy, alcohol consumption, total energy
Chang/2005/Sweden[18]	P-B, 597 NHL, 497 controls	Self-completed FFQ-137, validated	ICD	Red meat: >1.6 vs. <0.8 servings/day, fried red meat: >0.3 vs. <0.07 servings/day	1.2 (0.8–1.7), 1.5 (1.0–2.1)	Age, sex
Cross/2006/USA[19]	P-B, 458 NHL, 383 controls	Self-completed FFQ-117, validated	Histological	Red meat: Q4 vs. Q1, processed meat: Q4 vs. Q1	1.10 (0.67–1.81), 1.18 (0.74–1.89)	Age, sex, study site, physical activity, total caloric intake, alcohol consumption
Talamini/2006/Italy[20]	H-B, 190 NHL, 484 controls	Interviewer FFQ-63 validated	ICD	Red meat: 3.25 vs. 1.6 servings/week, processed meat: 3.5 vs. 1.5 servings/week	0.84 (0.50–1.40), 1.04 (0.63–1.72)	Age, gender, center, education, place of birth, HCV test, total energy intake
Hu/2008/Canadia[22]	P-B, 1666 NHL, 5039 controls	Self-completed FFQ-60, validated	Histological	Red meat: Q4 vs. Q1, processed meat: Q4 vs. Q1	1.1 (0.9–1.3), 1.2 (0.9–1.4)	Age, province, education, BMI, alcohol use, smoking, total of vegetable and fruit intake, and total energy intake

Author/Year/Country	Study Characteristics	Type of Questionnaire	Case Ascertainment	Exposure Details (Highest vs. Lowest)	RR (95% CI) (Highest vs. Lowest)	Adjustments
Chiu/2008/USA[21]	P-B, 385 NHL, 1432 controls	Self-completed FFQ-30, NA	Histological	Processed meat:>4 vs. <2 times/week	1.4 (0.7–2.7), 0.9 (0.5–1.6)	Age, sex, type of respondent, family history of cancer, BMI
Hu/2011/European[23]	P-B, 1666 NHL, 5039 controls	Self-completed FFQ	Histological	Processed meat: >5.4 vs. 0.9 servings/week	1.2 (0.9–1.4)	Age, province, education, BMI sex, alcohol use, smoking, total vegetable and fruit intake, and total energy intake
Aschebrook-Kilfoy/ 2012/USA[25]	P-B, 387 NHL, 535 controls	Mailed HHHQ, validated	Case ascertainment system	Red meat: 61.8 vs. 41.2 g/ 1000 kcal/day, processed meat: 13.1 vs. 6.2 g/ 1000 kcal/day	1.5 (1.1–2.2), 1.3 (0.9–1.9)	Age, sex, education level, and total energy intake
Balasubramaniam/ 2013/India[27]	H-B, 390 NHL, 1383 controls	Self-administered questionnaire, NA	Histological	Red meat: high vs. low	3.8 (2.8, 5.2)	Age, education
Charbonneau/2013/ USA[28]	H-B, 603 NHL, 1007 controls	Self-administered FQ-103, validated	Histological	Red meat: >50.1 vs. <19.5 servings/month, processed meat: >6.0 vs. <0.9 servings/month	1.07 (0.75–1.53), 1.37 (1.02–1.83)	Age, sex, total energy, residence
De Stefani/2013/ Uruguay[29]	H-B, 369 NHL 3606 controls	Interviews and questionnaire	Histological	Red meat: T3 vs. T1, processed meat: T3 vs. T1	1.25 (0.92–1.69), 0.95 (0.72–1.25)	Age, sex, residence, urban/rural status, education, BMI, smoking, alcohol drinking, mate consumption, total vegetable and fruit intake, and total energy
Ollberding/2013/ USA[30]	P-B, 336 NHL, 460 controls	Self-completed FFQ-117, validated	Histological	Beef: >52.4 vs. <30.6 g/ 1000 kcal/day, sausage: >2.7 vs. 0 g/1000 kcal/ day	1.5 (1.1–2.2), 1.5 (1.0–2.1)	Age, sex, education, total energy intake
Cohort						
Chiu/1996/USA[11]	IWHS: F N = 98,030, 104 NHL	Self-administered, FFQ-126, validated	Cancer registries	Red meat: >36 vs. <22 servings/month, processed meat: >6 vs. <4 servings/month	1.73 (1.01–2.97), 1.11 (0.68–1.79)	Age, total energy intake
Zhang/1999/USA[13]	NHS, F N = 88,410, 199 NHL	Self-administered, FFQ-126, validated	Self-report or death registry	Beef, pork, or lamb: 1 serving/day vs. <3 servings/month	2.2 (1.1–4.4)	Age, total energy, length of follow-up, geographic region, cigarette smoking, and height

Author/Year/Country	Study Characteristics	Type of Questionnaire	Case Ascertainment	Exposure Details (Highest vs. Lowest)	RR (95% CI) (Highest vs. Lowest)	Adjustments
Rohrmann/2011/Europe[24]	EPIC, N = 410,411, 1334 NHL	Self-completed FFQ, validated	Cancer registries	Red meat: ≥80 vs. <20 g/day, processed meat: ≥80 vs. <20 g/day	1.01 (0.82–1.26), 1.06 (0.82–1.37)	Age, energy, alcohol, education, fruits, vegetables, and smoking
Daniel/2012/USA[26]	NIH-AARP Diet and Health Study, N = 302,162, aged 50–71, N = 302,162, 3611 NHL	Self-completed FFQ-124, validated	Cancer registries	Red meat: 48.1 vs. 6.8 g/1000 kcal/day, processed meat: 23.6 vs. 2.2 g/1000 kcal/day	1.01 (0.90–1.14), 0.99 (0.89–1.11)	Age, sex, education, marital status, family history of cancer, race, BMI, smoking, physical activity, total energy intake, alcohol intake, and fruit and vegetable consumption

BMI = body mass index, F = female, FFQ = food frequency questionnaire, H-B = hospital-based case–control study, HCV = hepatitis C virus, HHHQ = Health Habits and History Questionnaire, IWHS = Iowa Women's Health Study, M = male, NA = data not available, NHL = Non-Hodgkin lymphoma, NHS = Nurses' Health Study, P-B = population-based case–control study.

1.68–3.26 and fried meat: SRR = 1.27; 95% CI, 1.01–1.63), but this was based on only two[12,29] and three studies,[13,18,19] respectively (Suppl. Table 2, http://links.lww.com/MD/A508). The risk of NHL was not positively associated with the intake of any other meat items, such as bacon, barbecued/grilled/broiled meat, or hamburgers. As an example, 4 individual studies[11,12,15,30] reported an association between beef intake and NHL risk. They yielded an SRR of 1.30 (95% CI, 0.97–1.74; $P_{\text{heterogeneity}} = 0.186$; $I^2 = 35.2\%$).

DISCUSSION

This detailed meta-analysis found that red and processed meat intake is associated with an increased risk of NHL. The estimated increase in risk found for high versus low consumption was 32% for red meat and 17% for processed meat. There was significant heterogeneity between studies for both red and processed meat intake. The findings were consistent with those obtained from linear dose–response meta-analysis. In nonlinear models, NHL risk appeared to increase approximately linearly with increasing intake of red meat, whereas there was evidence of nonlinearly of risk with increasing intake of processed meat.

Our findings are consistent with those of a previous much smaller meta-analysis of 3 cohort and 8 case–control studies which found a positive association between red and processed meat intake and the risk of NHL.[6] Our results, based on 16 case–control and 4 prospective cohort studies, are as striking. We examined the nature of the dose response relationship between consumption of red and processed meat and NHL risk in greater detail than did the previous meta-analysis, and found a positive dose–response relationship with increasing dietary red and processed meat intake. The Iowa Women's Health Study (IWHS) found that greater consumption of red meat (RR = 1.98; 95% CI, 1.13–3.47; *P* for trend = 0.02), and hamburgers in particular (RR = 2.35; 95% CI, 1.23–4.48; *P* for trend = 0.02) was associated with an increased risk of NHL.[11] Similarly, the Nurse's Health Study reported an increased risk of NHL with greater red meat intake (*P* for trend = 0.002).[13] In contrast, the European Prospective Investigation into Cancer and Nutrition (EPIC)[24] and the NIH-AARP Diet and Health Study[26] found no consistent associations between red and processed meat consumption and NHL risk.

Our meta-analysis found that red and processed meat consumption was significantly associated with an increased risk of NHL in case–control, but not in cohort, studies. Case–control studies are more susceptible to recall, particularly dietary recall, and selection biases, than are cohort studies. Information on dietary exposure was obtained after NHL had been diagnosed in the case–control studies included in our meta-analysis. These data may have been confounded by recall bias and inaccurate estimation of meat intake. Therefore, the finding that red and processed meat consumption is associated with an increased NHL risk should be treated with caution.

We undertook separate analyses of the risks for subtypes of NHL. We found no statistically significant associations between red and processed meat consumption and subtypes of NHL, except for that between processed meat consumption and DLBCL. However, these analyses were based on a maximum of 5 studies and may have lacked the power necessary to detect some associations. Clearly, further larger studies addressing this topic are required. Similar caution is appropriate when considering our findings on the relationship between red and processed meat consumption and the risk of NHL according to sex. A maximum of 4 studies were used for this analysis. For processed

TABLE 2. Stratified Meta-Analyses of Intake of Red and Processed Meat and Non-Hodgkin Lymphoma Risk

Subgroups	Red Meat				Processed Meat			
	Studies, n	SRR (95% CI)	P_h, I^2 (%)	P_d	Studies, n	SRR (95% CI)	P_h, I^2 (%)	P_d
All	17	1.32 (1.12–1.55)	<0.001, 79.0		16	1.17 (1.07–1.29)	0.057, 37.1	
Design								
Cohort	4	1.17 (0.92–1.49)	0.042, 63.4	0.825	3	1.07 (0.97–1.19)	0.986, 0	0.321
Case–control	13	1.34 (1.09–1.65)	<0.001, 79.6		13	1.21 (1.07–1.36)	0.06, 39.2	
P-B	6	1.18 (1.06–1.31)	0.444, 0	0.482	9	1.23 (1.06–1.42)	0.039, 49.2	0.626
H-B	7	1.48 (0.97–2.24)	<0.001, 86.7		4	1.13 (0.93–1.37)	0.371, 6.3	
Sex				0.321				0.251
Male	3	2.12 (0.80–5.59)	<0.001, 90.9		2	1.50 (0.98–2.31)	0.324, 0	
Female	4	1.61 (1.06–2.45)	0.200, 35.4		4	1.00 (0.69–1.45)	0.132, 46.5	
Country of origin				0.808				0.606
Europe	4	1.06 (0.90–1.24)	0.613, 0		4	1.18 (1.02–1.36)	0.468, 0	
USA	9	1.19 (1.05–1.35)	0.067, 45.3		10	1.19 (1.04–1.36)	0.018, 53.4	
South America	2	1.65 (0.99–2.75)	0.194, 38.9		2	1.00 (0.77–1.29)	0.459, 0	
Asia	2	1.95 (0.52–7.27)	<0.001, 96.7		0			
Type of FFQ, validated				**0.09**				0.367
Yes	11	1.14 (1.03–1.26)	0.120, 33.8		13	1.19 (1.07–1.33)	0.028, 47.7	
No	6	1.74 (1.03–2.91)	<0.001, 88.3		3	1.02 (0.82–1.27)	0.625, 0	
Study quality score				**0.087**				0.653
High	14	1.15 (1.04–1.26)	0.133, 29.7		15	1.17 (1.06–1.29)	0.045, 40.1	
Low	3	1.79 (0.80–3.98)	<0.001, 94.0		1	1.30 (0.90–1.90)	—	
Adjustments								
BMI, yes	4	1.13 (0.95–1.33)	0.104, 51.3	0.636	6	1.05 (0.93–1.20)	0.148, 36.8	**0.018**
No	13	1.37 (1.09–1.71)	<0.001, 80.6		10	1.32 (1.19–1.47)	0.652, 0	
Smoking, yes	7	1.15 (1.00–1.32)	0.081, 44.6	0.786	6	1.10 (1.01–1.19)	0.728, 0	0.222
No	10	1.36 (1.02–1.79)	<0.001, 84.4		10	1.23 (1.05–1.44)	0.049, 45.7	
Total energy intake, yes	11	1.17 (1.05–1.31)	0.09, 38.8	0.277	12	1.17 (1.04–1.31)	0.019, 51.7	0.846
No	6	1.57 (1.00–2.48)	<0.001, 89.4		4	1.18 (0.98–1.41)	0.516, 0	
Vegetable and fruit, yes	5	1.05 (0.97–1.15)	0.641, 0	**0.051**	4	1.10 (1.00–1.20)	0.477, 0	0.356
No	12	1.47 (1.14–1.90)	<0.001, 80.8		12	1.21 (1.06–1.39)	0.074, 38.0	
Alcohol use, yes	8	1.08 (1.00–1.18)	0.370, 3.7	0.222	8	1.17 (1.05–1.30)	0.137, 35.2	0.902
No	9	1.48 (1.06–2.07)	<0.001, 84.2		8	1.18 (0.98–1.42)	0.068, 45.1	

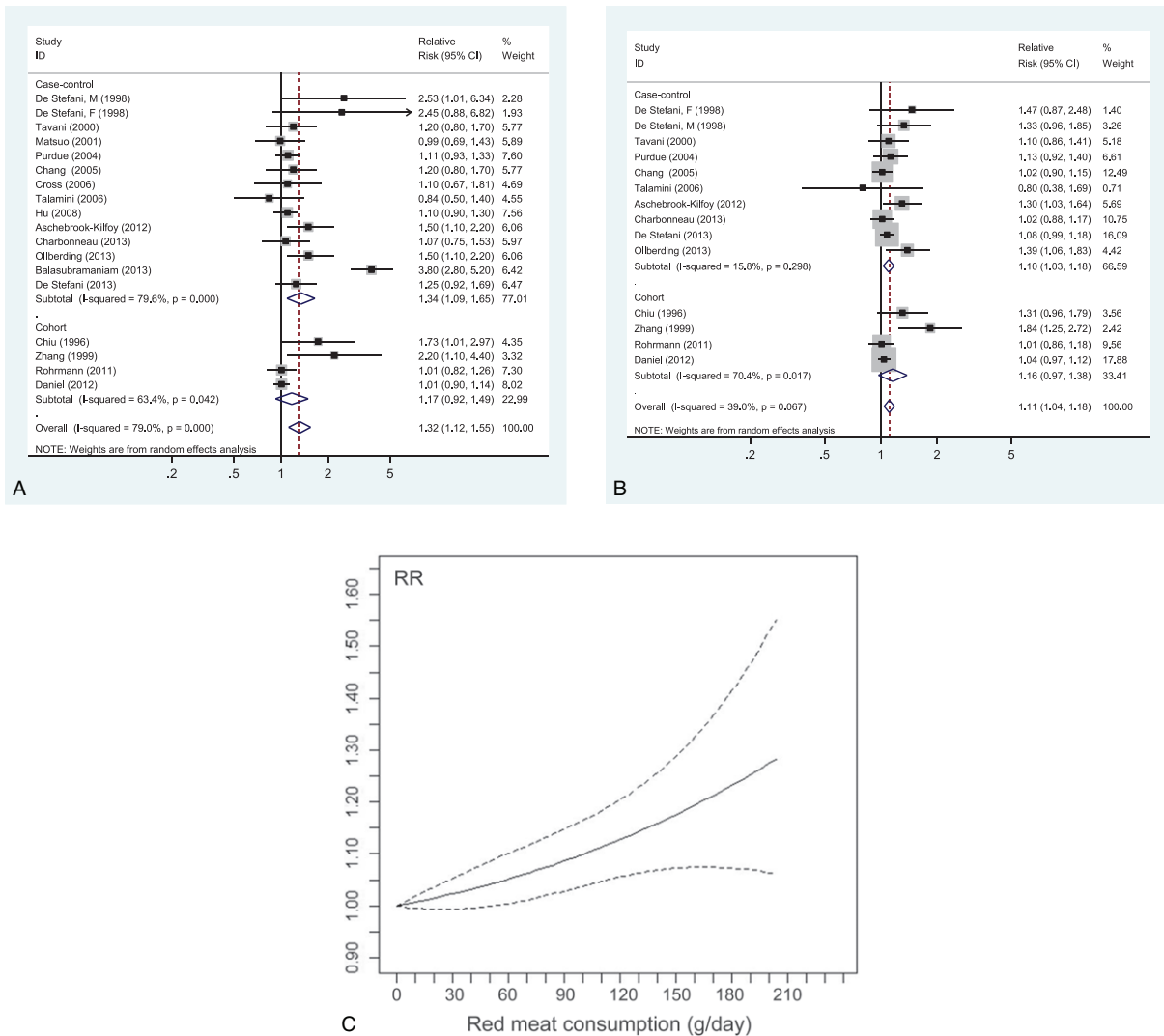Bold indicate a statistical significance at p<0.1

FIGURE 2. The summary risk association between red meat intake and risk of non-Hodgkin lymphoma according to (A) the highest versus lowest intake analysis; (B) linear dose–response analysis (per 100 g/day increment); (C) nonlinear dose–response analysis based on the best-fitting 2-term fractional polynomial regression model.

meat consumption, we found an association in both men and women, but for red meat, we found an association only in women.

A number of mechanisms to explain how red and processed meat intake might increase the risk of malignancies, including NHL, have been proposed. Known mutagens, such as HCAs and PAHs, are found in high concentrations in well-done grilled and pan fried meat. HCAs may be immunotoxic.[41] They have been found to increase the NHL risk in rodent models[28,42] and in a human study.[43] High saturated fat and animal protein content, as found in red and processed meat, has been positively associated with NHL risk in some studies;[11,17] although others have found the converse[19] or a lack of any association.[13,16] Other potential mechanisms which might underlie an increased risk of NHL risk with red and processed meat consumption, involve NOCs, which have been linked to the risk of lymphoma in humans.[44,45]

In comparison of the previous meta-analysis,[6] ours has the advantage that it included more observational studies, allowing

us to undertake both high versus low exposure and linear and nonlinear dose–response meta-analyses. In addition, we conducted a rigorous quality assessment. Finally, by undertaking a sensitivity analysis, we were able to explore the source of heterogeneity between studies.

However, our meta-analysis has several limitations. We found there was considerable heterogeneity between studies, especially concerning red meat consumption. Based on the subgroup meta-regression analysis, we found that the type of FFQ, study quality score and the adjustments made for vegetable and fruits intake might partially account for this. With regards to the association between processed meat consumption and NHL risk, we found evidence that this might be partially a consequence of adjustments made for BMI. We also found there to be considerable heterogeneity between studies in the dose–response analyses of processed meat consumption; this might have partially been a consequence of the conversions made to the intake units. These were variously reported as g/day,
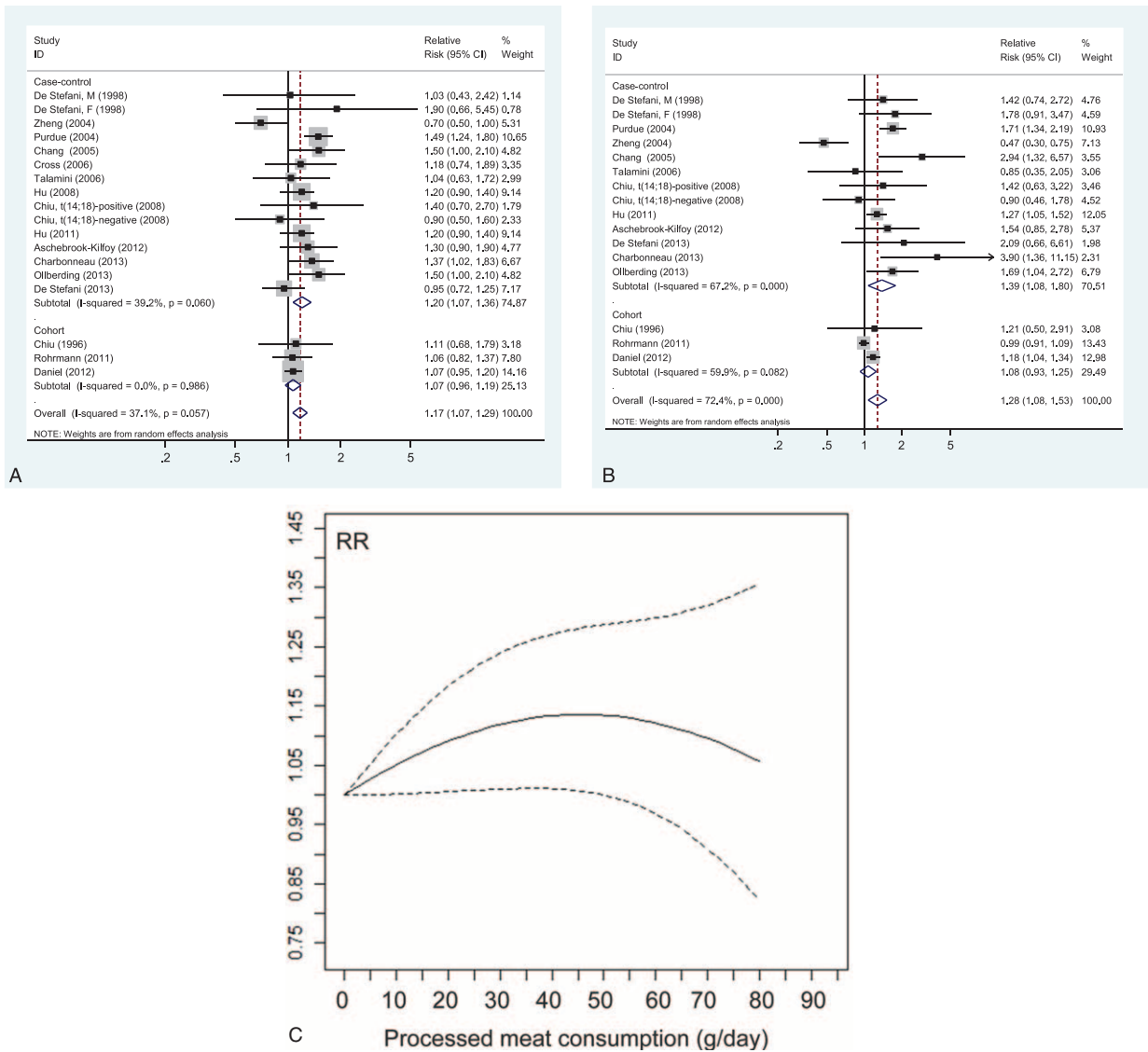
FIGURE 3. The summary risk association between processed meat intake and risk of non-Hodgkin lymphoma according to (A) the highest versus lowest intake analysis; (B) linear dose–response analysis (per 50 g/day increment); (C) nonlinear dose–response analysis based on the best-fitting 2-term fractional polynomial regression model.

servings/week, g/1000 kcal/day, and servings per month. We converted all of these to g/day by assuming that a serving corresponds to 50 g of processed meat.

A further consideration is that inaccurate assessments of red and processed meat intake could have led to overestimations of the range of intakes, and thus underestimation of the magnitude of the relationship between dietary intake and the risk of NHL.[46,47] Semiquantitative FFQs were used for dietary assessment in all studies. However, these had not all been validated. Subgroup analyses showed that use of validated versus nonvalidated FFQs significantly affected the association between red meat intake and NHL risk. Another challenge we had to deal with was the variation in the definitions and categorization of red and processed meat between studies and in the analytical methods used in different studies. One

example of this is the various ways that consumption was quantified: portions per week, times per month, grams per day, or servings per day.

Residual confounders are always a concern in observational studies. For example, individuals who eat more red and processed meat may also have higher rates of smoking, alcohol use and obesity, and eat less vegetable and fruit. Subgroup analysis according to studies controlled for these factors, we found that vegetable and fruit intake was a significant factor for red meat intake and NHL risk and that BMI was a significant factor for processed meat consumption and NHL risk, suggesting that vegetable and fruit intake and BMI are potential confounding factors. Only 1 study considered the possible confounding effect of infection with the hepatitis B and C viruses,[14] both of which are known to associated with an
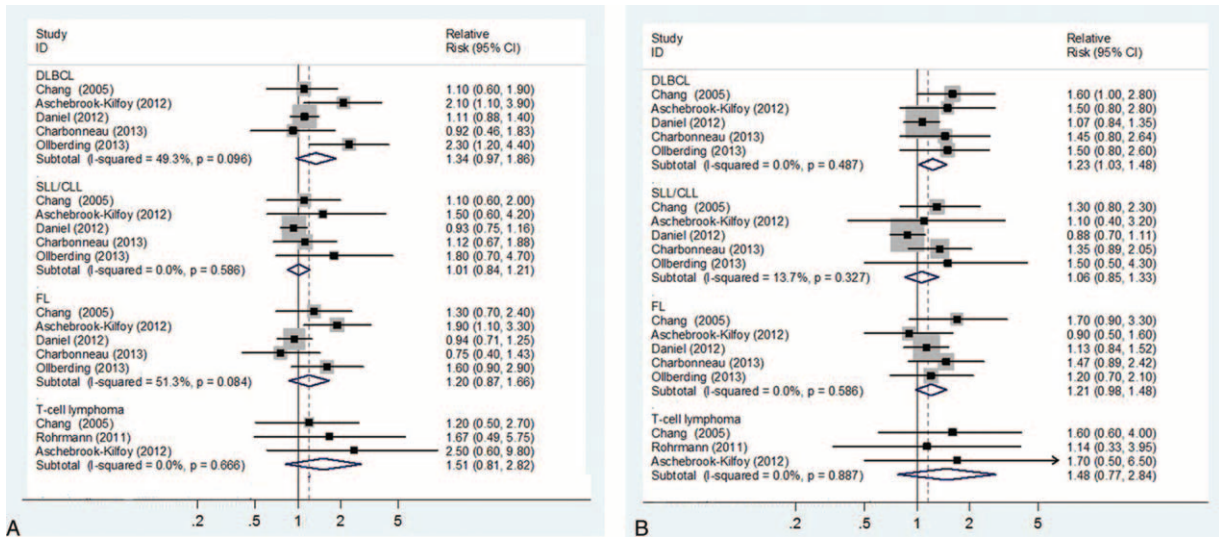
FIGURE 4. Intake of red (A) and processed meat (B) and risk of the subtypes of Non-Hodgkin lymphoma. FL, follicular lymphoma, DLBCL, diffuse large B-cell lymphoma, SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia.

increased risk of NHL.[20,48] Other confounding factors cannot be excluded.

Finally, as is the case for all meta-analysis, there is the possibility of publication bias, since small studies with negative results tend not to be published. However, the funnel plot analysis and formal statistical tests did not provide evidence for this.

In conclusion, our data suggest that heavy consumption of red and processed meat may increase the risk of NHL. However, because the effect was only found in case–control studies and might be a consequence of biases and confounding factors, large scale, prospective epidemiological studies that control for possible confounders and examine the incidence of NHL in relation to the level of meat consumption are required.

REFERENCES

1. Karami K, Cheraghi M, Amori N, et al. Common cancers in Khuzestan province, south west of Iran, during 2005–2011. *Asian Pac J Cancer Prev.* 2014;15:9475–9478.

2. Ekstrom-Smedby K. Epidemiology and etiology of non-Hodgkin lymphoma—a review. *Acta Oncol (Stockholm, Sweden).* 2006;45:258–271.

3. Larsson SC, Wolk A. Body mass index and risk of non-Hodgkin's and Hodgkin's lymphoma: a meta-analysis of prospective studies. *Eur J Cancer.* 2011;47:2422–2430.

4. Kamper-Jorgensen M, Rostgaard K, Glaser SL, et al. Cigarette smoking and risk of Hodgkin lymphoma and its subtypes: a pooled analysis from the International Lymphoma Epidemiology Consortium (InterLymph). *Ann Oncol.* 2013;24:2245–2255.

5. Chen GC, Lv DB, Pang Z, et al. Fruits and vegetables consumption and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Int J Cancer.* 2013;133:190–200.

6. Fallahzadeh H, Cheraghi M, Amoori N, et al. Red meat intake and risk of non-Hodgkin lymphoma: a meta-analysis. *Asian Pac J Cancer Prev.* 2014;15:10421–10425.

7. Abid Z, Cross AJ, Sinha R. Meat dairy and cancer. *Am J Clin Nutr.* 2014;100(Suppl. 1):386S–393S.

8. Ghoshal A, Preisegger KH, Takayama S, et al. Induction of mammary tumors in female Sprague-Dawley rats by the food-derived carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine and effect of dietary fat. *Carcinogenesis.* 1994;15:2429–2433.

9. Steineck G, Gerhardsson de Verdier M, Overvik E. The epidemiological evidence concerning intake of mutagenic activity from the fried surface and the risk of cancer cannot justify preventive measures. *Eur J Cancer Prev.* 1993;2:293–300.

10. Rohrmann S, Hermann S, Linseisen J. Heterocyclic aromatic amine intake increases colorectal adenoma risk: findings from a prospective European cohort study. *Am J Clin Nutr.* 2009;89:1418–1424.

11. Chiu BC, Cerhan JR, Folsom AR, et al. Diet and risk of non-Hodgkin lymphoma in older women. *JAMA.* 1996;275:1315–1321.

12. De Stefani E, Fierro L, Barrios E, et al. Tobacco, alcohol, diet and risk of non-Hodgkin's lymphoma: a case-control study in Uruguay. *Leuk Res.* 1998;22:445–452.

13. Zhang S, Hunter DJ, Rosner BA, et al. Dietary fat and protein in relation to risk of non-Hodgkin's lymphoma among women. *J Natl Cancer Inst.* 1999;91:1751–1758.

14. Tavani A, La Vecchia C, Gallus S, et al. Red meat intake and cancer risk: a study in Italy. *Int J Cancer.* 2000;86:425–428.

15. Matsuo K, Hamajima N, Hirose K, et al. Alcohol, smoking, and dietary status and susceptibility to malignant lymphoma in Japan: results of a hospital-based case-control study at Aichi Cancer Center. *Jpn J Cancer Res.* 2001;92:1011–1017.

16. Purdue MP, Bassani DG, Klar NS, et al. Dietary factors and risk of non-Hodgkin lymphoma by histologic subtype: a case-control analysis. *Cancer Epidemiol Biomarkers Prev.* 2004;13:1665–1676.

17. Zheng T, Holford TR, Leaderer B, et al. Diet and nutrient intakes and risk of non-Hodgkin's lymphoma in Connecticut women. *Am J Epidemiol.* 2004;159:454–466.

18. Chang ET, Smedby KE, Zhang SM, et al. Dietary factors and risk of non-Hodgkin lymphoma in men and women. *Cancer Epidemiol Biomarkers Prev.* 2005;14:512–520.

19. Cross AJ, Ward MH, Schenk M, et al. Meat and meat-mutagen intake and risk of non-Hodgkin lymphoma: results from a NCI-SEER case-control study. *Carcinogenesis.* 2006;27:293–297.

20. Talamini R, Polesel J, Montella M, et al. Food groups and risk of non-Hodgkin lymphoma: a multicenter, case-control study in Italy. *Int J Cancer.* 2006;118:2871–2876.

21. Chiu BC, Dave BJ, Ward MH, et al. Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma. *Cancer Causes Control.* 2008;19:859–867.

22. Hu J, La Vecchia C, DesMeules M, et al. Meat and fish consumption and cancer in Canada. *Nutr Cancer.* 2008;60:313–324.

23. Hu J, La Vecchia C, Morrison H, et al. Salt, processed meat and the risk of cancer. *Eur J Cancer Prev.* 2011;20:132–139.

24. Rohrmann S, Linseisen J, Jakobsen MU, et al. Consumption of meat and dairy and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2011;128:623–634.

25. Aschebrook-Kilfoy B, Ollberding NJ, Kolar C, et al. Meat intake and risk of non-Hodgkin lymphoma. *Cancer Causes Control.* 2012;23:1681–1692.

26. Daniel CR, Sinha R, Park Y, et al. Meat intake is not associated with risk of non-Hodgkin lymphoma in a large prospective cohort of U.S. men and women. *J Nutr.* 2012;142:1074–1080.

27. Balasubramaniam G, Saoba S, Sarade M, et al. Case-control study of risk factors for Non-Hodgkin lymphoma in Mumbai, India. *Asian Pac J Cancer Prev.* 2013;14:775–780.

28. Charbonneau B, O'Connor HM, Wang AH, et al. Trans fatty acid intake is associated with increased risk and n3 fatty acid intake with reduced risk of non-Hodgkin lymphoma. *J Nutr.* 2013;143:672–681.

29. De Stefani E, Ronco AL, Deneo-Pellegrini H, et al. Meat, milk and risk of lymphoid malignancies: a case-control study in Uruguay. *Nutr Cancer.* 2013;65:375–383.

30. Ollberding NJ, Aschebrook-Kilfoy B, Caces DB, et al. Phytanic acid and the risk of non-Hodgkin lymphoma. *Carcinogenesis.* 2013;34:170–175.

31. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA.* 2000;283:2008–2012.

32. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed June 15, 2012.

33. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–188.

34. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557–560.

35. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol.* 1992;135:1301–1309.

36. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *BMC Cancer.* 2006;6:40–57.

37. World Cancer Research Fund/American Institute for Cancer Research. Policy and Action for Cancer Prevention. Food, Nutrition, and Physical Activity: a Global Perspective. Washington, DC: AICR; 2007.

38. Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. *Stat Med.* 2000;19:1831–1847.

39. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clin Res Ed).* 1997;315:629–634.

40. Cross AJ, Leitzmann MF, Gail MH, et al. A prospective study of red and processed meat intake in relation to cancer risk. *PLoS Med.* 2007;4:e325.

41. Davis DA, Archuleta MM, Born JL, et al. Inhibition of humoral immunity and mitogen responsiveness of lymphoid cells following oral administration of the heterocyclic food mutagen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) to B6C3F1 mice. *Fundam Appl Toxicol.* 1994;23:81–86.

42. Sorensen IK, Mortensen A, Kristiansen E, et al. Short-term carcinogenicity testing of 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) and 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) in E(mu)-pim-1 transgenic mice. *Carcinogenesis.* 1996;17:2221–2227.

43. Morton LM, Wang SS, Cozen W, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes. *Blood.* 2008;112:5150–5160.

44. Kilfoy BA, Ward MH, Zheng T, et al. Risk of non-Hodgkin lymphoma and nitrate and nitrite from the diet in Connecticut women. *Cancer Causes Control.* 2010;21:889–896.

45. Aschebrook-Kilfoy B, Ward MH, Dave BJ, et al. Dietary nitrate and nitrite intake and risk of non-Hodgkin lymphoma. *Leuk Lymphoma.* 2013;54:945–950.

46. Prentice RL. Dietary assessment and the reliability of nutritional epidemiology reports. *Lancet.* 2003;362:182–183.

47. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122:51–65.

48. Dong HJ, Ni LN, Sheng GF, et al. Risk of hepatitis B virus (HBV) reactivation in non-Hodgkin lymphoma patients receiving rituximab-chemotherapy: a meta-analysis. *J Clin Virol.* 2013;57:209–214.