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Review Article

Coffee and the Risk of Lymphoma: A Meta-analysis Article

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Abstract

Background: Coffee is implicated in the susceptibility to several cancers. However, the association between coffee and lymphoma remains unclear. This meta-analysis aimed to assess quantitatively the association between coffee and the incidence of lymphoma.

Methods: A literature search was performed for cohort and case-control studies published using PubMed, Cochrane, and EMBASE databases. Studies were included if they reported relative ratios (RR) and corresponding 95% confidence intervals (CIs) of lymphoma with respect to coffee consumption. Pooled relative risk (RR) and its 95% confidence interval (CI) were calculated. All *P* values are two tailed

Results: Seven studies met the inclusion criteria, which included three cohort and four case-control studies. Compared with did not or seldom drink coffee per day, being no significantly association between coffee and risk of lymphoma (pooled RR: 1.05, 95%CI: 0.89-1.23). In the subgroup analysis, no significant association between coffee and lymphoma risk was detected not only in different study types (cohort studies RR: 1.29; 95% CI, 0.92-1.80; case control studies RR: 0.99; 95% CI, 0.82-1.99) but also in different regions (Europe RR: 1.21; 95% CI: 0.99-1.47; USA RR: 0.85; 95% CI, 0.62-1.15; Asia RR: 1.08, 95% CI: 0.84-1.40) and coffee consumption status (≥4cups/d 1.03, 95% CI: 0.69–1.56; ＜4cups/d RR: 1.06, 95% CI: 0.89- 1.26). The funnel plot revealed no evidence for publication bias.

Conclusion: There was no sufficient evidence to support coffee consumption association with the risk of lymphoma. Further well-designed large-scaled cohort studies are needed to provide conclusions that are more definitive.

Keywords: Lymphoma, Coffee, Cohort study, Case-control study, Meta-analysis

Introduction

Lymphoma is a type of highly heterogeneous hematological malignancy, which includes two major categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The incidence and mortality rates of lymphoma increased steadily in recent years all over the world especially in the developed countries (1, 2). Investigations focusing on etiology of lymphomas have progressed: infections of pathogenic microorganism, immune-modulatory defects, obesity, autoimmune diseases and environmental exposure seem to be most established increasing the risk of lymphoma (3, 4). However, the remaining reasons for the increasing cases of lymphoma are largely unclear.

Coffee is one of the most widely consumed beverages worldwide, which contains a wide variety of phytochemicals. A number of epidemiological studies for possible associations between coffee and cancers of the breast, prostate, liver, colon, and rectum have been reported (5, 6).

Among these, the epidemiologic evidence on the association between coffee consumption and lymphma risk has not yet been summarized, we

conducted a meta-analysis to summarize quantitatively the results from cohort and case– control studies on this issue.

Methods

Data sources and searches

The relevant studies from the search engines of PubMed, EMBASE, and Cochrane (from 1966 to May 2014) were independently screened by two investigators (Tian-Jie Han and Wang Ling), using the Medical Subject Heading (MeSH) terms 'coffee', 'lymphoma', with the language limit in English and Chinese. Furthermore, we reviewed the reference lists of retrieved articles to search for more studies.

Inclusion and exclusion criteria

This meta-analysis study were included the following criteria: 1) the study design was case-control or cohort; 2) the exposure of interest was coffee consumption; 3) lymphoma was the outcomes of interest; 4) relative risk ratio (RR) or risk hazard ratio (HR) in cohort studies or odds ratio (OR) in case-control studies with their 95% confidence intervals (CIs) were reported or can be calculated. If sequential or multiple publications from the same data occurred, the publication that reported data from the largest or most recent study was included.

Data extraction

Two independently investigators (Jun-Shan Li and Wang Ling) extracted the data according to the MOOSE guideline (7). The information of each study was extracted as following: first author's last name, continents/country where the study was conducted, year of publication, numbers of cases, mean age of cases and controls, diagnostic criteria, selection of the control group, RRs of lymphoma and corresponding 95% CIs for coffee, and covariates (including age, sex, smoking and BMI) adjusted in the statistical analysis. Discrepancies were resolved by discussion with a third investigator (Wang Ling), and a consensus was reached.

Assessment of study quality

The Newcastle-Ottawa Scale was used in study quality (range, 1–9 scores) (8), which contains three broad perspectives; namely, the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for cohort or case-control studies, respectively.

Statistical analysis

The study-specific most adjusted RR was used to compute a summary RR and its 95% CI. Study-specific estimates were combined using the Der Simonian and Laird random-effects model. The statistical heterogeneity among the studies was estimated by the Chi-square-test based Q-statistic (9), and a significant Q-statistic (P<0.10) indicated heterogeneity across the studies. The pooled RR was calculated by a fixed effect model (using the Mantel-Haenszel method) or a random effect model (using the DerSimonian and Laird method) according to the heterogeneity among studies (10, 11). Using Begg's funnel plot and Egger's test to assess the publication bias, and a P value of < 0.05 was considered as statistically significant (l2). All analyses were performed by using Stata version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Literature search and studies characteristics

Overall, 64 articles were identified; 51 articles were not eligible as they were not cohort or case-control studies, and six articles were excluded due to incomplete or insufficient data required for the meta-analysis (Fig. 1). Therefore, seven studies including three cohort (13-15) and four case-control (16-19) studies, were included in this meta-analysis. The characteristics of the studies are shown in Table 1.

The continents or countries were as follow: Asia (n = 1) (18), the United States of America (n =2) (17, 19), and Europe (n = 4) (13-16). The outcome was incidence of non-Hodgkin's lymphoma in four studies, the other three studies outcome

was incidence of lymphoma. In the studies, participants were asked about their coffee consumption, such as per day or times per week. Overall, 1513 cases with lymphoma were in seven studies. Among these studies, the ascertainment of outcome was based on a cancer registry in all studies. Potential confounders (at least for age) were controlled in all studies.

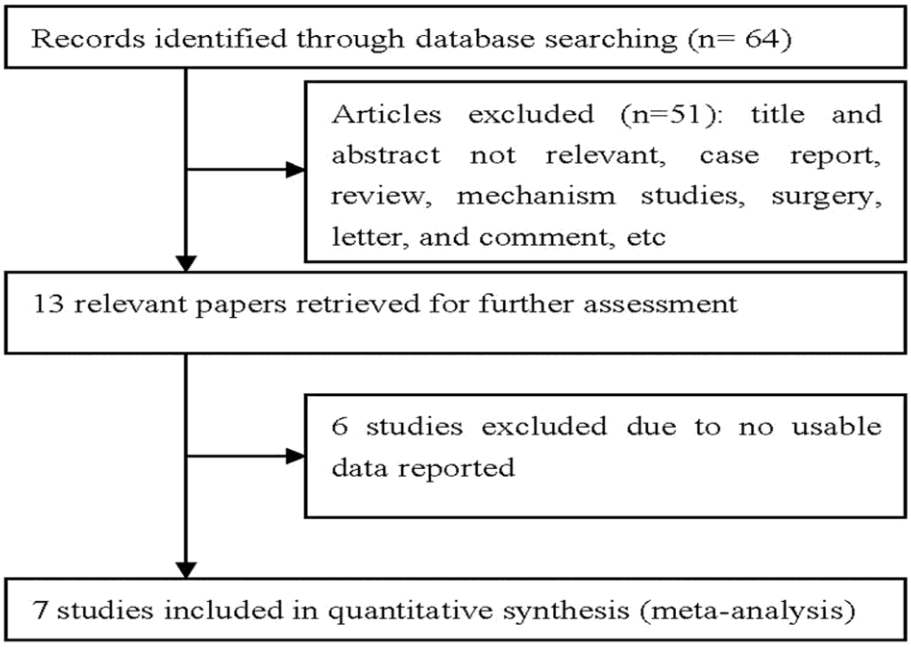

Fig. 1: Flow chart of study selection

Quality evaluation of included studies

The Newcastle-Ottawa Scale was adopted in our quality assessment. All groups of controls appeared to be selected based on convenience. The patients and controls were matched by age in all the studies. The full score was nine, and all studies scored six or higher (Table 1).

Main results of meta-analysis

In the analysis of all studies, the summary RR of lymphoma were 1.05 (95% CI 0.89 -1.23) in a random-effects model. There was no evidence for heterogeneity among the studies (Q=43.15, P=0.01 I^2=44.4%).

We conducted subgroup meta-analyses by geographic area and study design. The summary RRs (95% CI) of the associations between coffee and lymphoma risk was 1.29 (0.92-1.80) in cohort studies, and 0.99 (0.82-1.99) in case control studies (Fig. 2), which were similar to the association between coffee and lymphoma risk (Table 2). According to the meta-analysis by geographic area (Figure 3), there was no significant association between coffee and lymphoma risk in Europe regions (summary RR: 1.21; 95% CI: 0.99-1.47), and USA (summary RR: 0.85; 95% CI, 0.62-1.15). In addition, no association was found between coffee and lymphoma risk in Asian studies (summary RR: 1.08, 95% CI: 0.84-1.40), notably, coffee consumption status (i.e. ≥4cups/d and ＜4cups/d) was not associated with lymphoma risk (summary RR: 1.03, 95% CI: 0.69–1.56 and summary RR: 1.06, 95% CI: 0.89- 1.26, respectively). The summary RR and 95% CI between coffee and NHL is 0.96 (95% CI: 0.78–1.17) which was not statistically significant.

Table 1: Characteristics of the studies include in the meta-analysis

Reference	No. of cases (men/women)	Controls or cohort size (men/women)	Coffee consumption	Risk estimate (95% CIs)	Study quality	Adjustments
Cohort studies						
Norwegian(13)	NHL/HL 42	men 13,664 women 2,891	≤2 cups/day 3-4 cups/day 5-6 cups/day ≥7 cups/day	Men and Women 1.0 1.54 (0.68-3.52) 1.13 (0.43-2.91) 1.58 (0.55-4.56)	7	Age, sex, smoking
Norwegian (14)	NHL/HL men 40women 26	men 21,735 women 21,238	≤2 cups/day 3-4 cups/day 5-6 cups/day ≥7 cups/day	Men and Women 1.0 3.19(1.12-9.05) 1.86(0.63-5.47) 1.72(0.62-4.78)	7	Age, sex, smoking, Triglycerides, Wine/liquor consumption
Swnden(15)	NHL 111	Men 32,425 Women 32,178	< 1 cups/day 1–3 cups/day > 4 cups/day	Men and Women 1.0 0.67(0.36–1.25) 1.09(0.58–2.06)	7	Age, sex,BMI
Case-control Studies						
Italy(16)	NHL 429	1157	1 cups/day 2 cups/day 3 cups/day 4 cups/day 5 cups/day	Men and Women 1.1 (0.7–1.6) 1.1 (0.8–1.6) 1.0(0.7–1.6) 0.9 (0.5–1.6) 2.2 (1.3–3.8)	8	Age, sex, smoking, BMI
USA(17)	NHL White men and women 385	1432	<5 times/week 5-14times/week 15-28times/week >28 times/week	Men / Women 1.0 / 1.0 1.1 (0.6–1.9) / 2.0 (1.1–3.6) 0.9 (0.5–1.6) / 1.0 (0.5–1.9) 0.4 (0.2–0.8) / 1.2 (0.6–2.3)	8	Age, sex, race, smoking
Japenese(18)	NHL/HL 333	55904	Occasionally or less Everyday Unknown	Men / Women 1.0 / 1.0 1.07(0.82-1.39) / 1.18(0.83-1.66) NA / NA	7	Age, sex, smoking, drinking

USA(19)	NHL t(14;18)-positive：60 t(14;18)-negative：87	1075	＜9times/week 9–28times/week ＞28times/week	Positive 1.00.6 (0.3-1.2) 0.4 (0.2-0.7)	negative 1.0 0.9(0.5–1.7) 0.8 (0.4 – 1.4)	8	Age, sex, BMI

CI confidence interval; NHL Non-Hodgin lymphoma; HL Hodgin lymphoma ;BMI body mass index; NA, not applicable

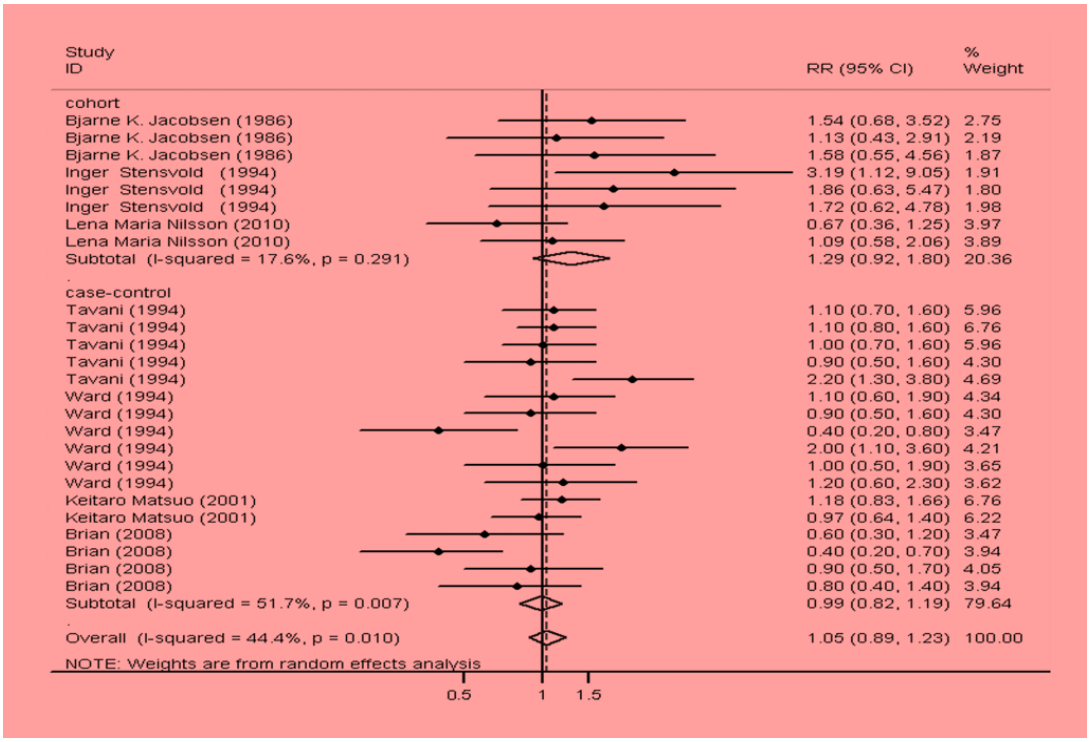

Fig. 2: Forest plot of the association between coffee and risk of lymphoma for studies by design

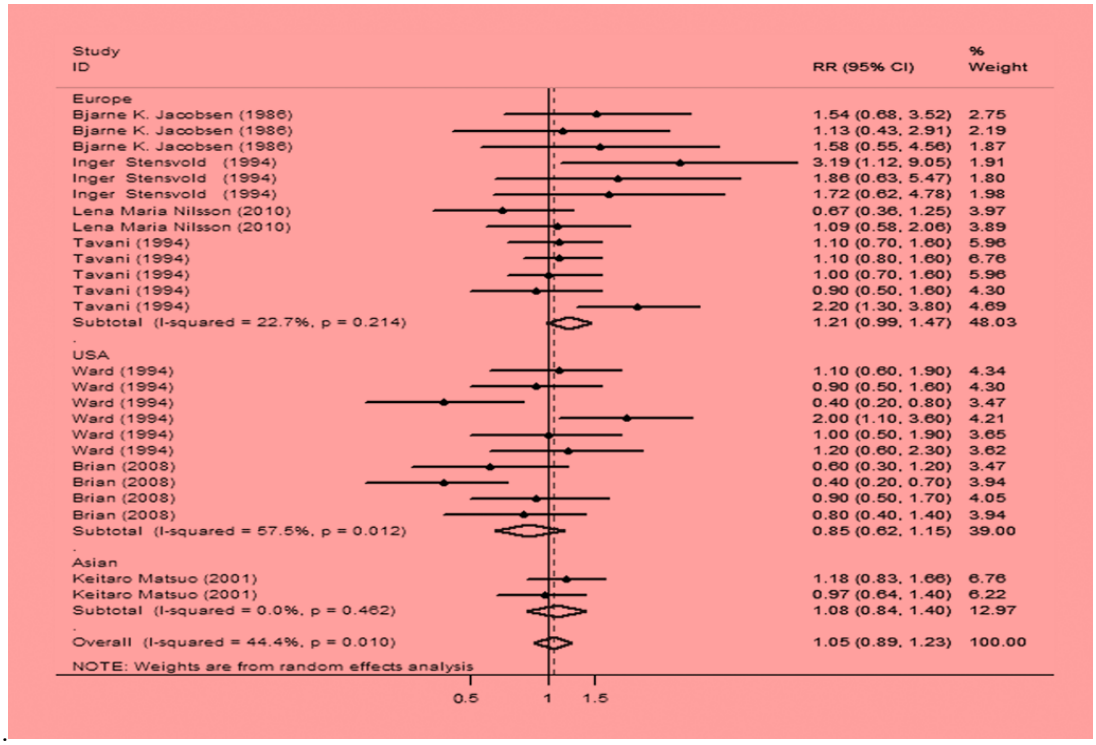

Fig. 3: Forest plot of the association between coffee and risk of lymphoma for studies by race

Table 2: Meta-analysis and sub-analyses of studies evaluating association between coffee and the risk of lymphoma

Groups	Number of studies	Adjusted Odds ratio (95% CI)	*P* value[a]
Design:			
Cohort(13,14,15)	3	1.29 (0.92-1.80)	= 0.138
case-control(16,17,18,19)	4	0.99 (0.82-1.19)	= 0.890
Race:			
Europe(13,14,15,16)	4	1.21 (0.99-1.47)	=0.062
USA(17,19)	2	0.85 (0.62-1.15)	= 0.283
Asian(18)	1	1.08 (0.84-1.40)	= 0.549
Cup:			
≥4cups/day	6	1.03(0.69-1.56)	= 0.876
<4cups/day	6	1.06 (0.89-1.26)	= 0.549
Everday	1	1.08 (0.84-1.40)	=0.549
Type：			
NHL(15,16,17,19)	4	0.96 (0.78-1.17)	=0.056
NHL/HL(13,14,18)	3	1.24 (0.99-1.54)	=0.651

[a]The method of DerSimonian and Laird random-effects model was used

Publication bias

There was no evidence for publication bias concerning the association between coffee and lymphoma risk using either the Egger's test (P=0.714) or visualization of the Begg's funnel plot (P =0.64) .

Discussion

To the best of our knowledge, this is the first meta-analysis assessing the association between coffee and lymphoma risk. The overall result suggests that coffee intake is not associated with the risk of lymphoma.

Coffee - one of the most widely consumed beverages worldwide- contains a wide variety of phytochemicals, such as CGAs, mela-noidins, caffeine, trigonelline and the diterpenes cafestol, kahweol, and many of which possess various properties including antioxidants and chemopreventive constituents which induce apoptosis and inhibit angiogenesis activity (20-22). Emerging evidence point outs an inverse association between coffee consumption and cancers of liver (23, 24), breast (25-27), colon and rectum (28, 29), whereas no association has reported for prostate (30-32), ovarian (33), pancreatic or gastric cancer (34, 35). In the present meta-analysis, although an Italian study (16) has suggested that coffee is a risk factor for lymphoma, there was no conclusive evidence on this association in our data analysis.

The present meta-analysis confirms the lack of association between coffee consumption and lymphoma. All of the observational studies included in this meta-analysis reported the results stratified by various pre-defined factors, such as age and sex. However, there is not enough controlling on confounders or known major risk factors of lymphoma. For example, we found that coffee consumption decreases the risk of diabetes (36) while it has previously been reported moderately increased risk of lymphoma (37). Therefore, without adjustment for diabetes (which was the case in all studies included) it may attenuate positive association towards a null. Conversely, coffee consumption tends to be related to other living habits such as smoking being reported to increase lymphoma risk. Thus, a failure to account for tobacco smoking status (which was the case in two studies (15, 19)) it may exaggerate any harm of coffee. Potential mechanisms, thereby, coffee may modulate lymphoma risk come into question, with both protective and adverse effects proposed. Coffee contains many bioactive compounds including phenolic acids with strong antioxidant properties and cafestol and kahweol with anticarcinogenic activity (38). Experimental evidence demonstrates that instant coffee protect mouse lymphoma cells from DNA-damage agents and gamma-radiation in vitro (39,40). Moreover, coffee consumption may correlate with lower circulating levels of inflammatory markers including chemokines (CX3CL1/fractalkine, CCL4/MIP-1b), cytokines (IFNg, sTNFRII), and basic fibroblast growth factor (FGF-2) linked to lymphoma pathogenesis (41-43). However, in hypertensive smokers, heavy coffee drinking is associated with augmented inflammatory factors such as IL-6 and PAI-1 levels (44). On the other hand, coffee also contains acrylamide, which has potential carcinogenic effects (45, 46).

Heterogeneity across studies is often in a meta-analysis. Certain degree of heterogeneity was observed given the between-study variation, such as race, study design, etc. However, meta-regression was adopted and no variables were identified as a potential contributor to heterogeneity. In a subgroup analysis stratified based on Asians and non-Asians. This may partially explain the above differences between Asians and non-Asians.

This meta-analysis has several limitations. First, most of the studies included were conducted in America and Europe, only one in Asia, none in Africa or South America. Second, misclassification of coffee consumption also should be taken into account. Most studies used the number of cups to assess coffee consumption. However, the size of cups may be different, more accurate questionnaires or other advanced methods as-

sessing coffee intake could be better estimated. Third, in any meta-analysis, the possibility of publication bias is of concern, because small studies with null results tend not to be published. Publication bias may have resulted in an overestimation of the association between coffee and risk of lymphoma. However, the results obtained from funnel plot analysis and formal statistical tests did not provide evidence for such a bias. The number of included studies is relatively small. Thus, more studies, especially long-term prospective studies, on the association between coffee and lymphoma risk are needed to confirm the results.

Conclusion

Coffee consumption is not associated with the risk of lymphoma. Despite these possible limitations, the main strength of this meta-analysis is large number of cases and participants that enhanced the statistical power of the study. Although subgroup meta-analyses by geographic area and study design did minimize the heterogeneity of different studies, well-designed prospective studies will be needed conclude the association between coffee consumption and lymphoma risk.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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