Alcohol drinking and non-Hodgkin lymphoma risk: a systematic review and a meta-analysis

I. Tramacere1, C. Pelucchi1*, M. Bonifazi1, V. Bagnardi2,3, M. Rota2,4, R. Bellocco2,5, L. Scotti2, F. Isla6,7,8, G. Corrao2, P. Boffetta8,9, C. La Vecchia1,10 & E. Negri1

1Department of Epidemiology, Mario Negri Institute for Pharmacological Research, Milan; 2Department of Statistics, University of Milano-Bicocca, Milan; 3Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan; 4Department of Clinical Medicine and Prevention, Centre of Biostatistics for Clinical Epidemiology, University of Milano-Bicocca, Monza, Italy; 5Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; 6International Agency for Research on Cancer, Lyon, France; 7Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran; 8The Tisch Cancer Institute, Mount Sinai School of Medicine, New York, USA; 9International Prevention Research Institute, Lyon, France; 10Department of Occupational Health, University of Milano, Milan, Italy

Received 20 December 2011; revised 23 January 2012; accepted 24 January 2012

Background: Whether an association between alcohol drinking and non-Hodgkin lymphoma (NHL) risk exists is an open question. In order to provide quantification of the issue, we carried out a meta-analysis of published data.

Methods: We identified 21 case-control and 8 cohort studies, including a total of 18 759 NHL cases. We derived meta-analytic estimates using random-effects models, taking into account correlation between estimates.

Results: The overall relative risk (RR) of NHL for drinkers versus non-drinkers was 0.85 [95% confidence interval (CI) 0.79–0.91]. Compared with non-drinkers, the pooled RRs were 0.88 for light (≤1 drink per day), 0.87 for moderate (1 to <4 drinks per day), and 0.84 for heavy (≥4 drinks per day) alcohol drinking. There was no association for light drinkers in cohort studies, whereas for moderate and heavy drinkers, the RRs were similar in case–control (0.85 for moderate, 0.92 for heavy) and cohort (0.89 for moderate, 0.79 for heavy) studies. The inverse relation with alcohol consumption (drinkers versus non-drinkers) was similar in men (RR = 0.83) and women (RR = 0.86), but apparently stronger in studies from Asia (RR = 0.69) than other world areas (RR = 0.88).

Conclusion: This meta-analysis provides quantitative evidence of a favourable role of alcohol drinking on NHL risk, though the lack of a biological explanation suggests caution in the interpretation of results.

Key words: alcohol drinking, dose-risk relation, meta-analysis, non-Hodgkin lymphoma, systematic review

introduction

Whether an association between alcohol drinking and non-Hodgkin lymphoma (NHL) risk exists is an open question. The Monograph 96 of the International Agency for Research on Cancer (IARC), published in 2007, considered 5 cohort studies among heavy drinkers and 4 in the general population, and 16 case-control studies [1]. The IARC working group reported reduced risks of NHL in drinkers versus non-drinkers in a few studies and concluded that there was evidence suggesting lack of carcinogenicity of alcohol drinking on NHL. A similar conclusion was reached by a subsequent IARC working group [2]. Furthermore, the World Cancer Research Fund (WCRF) Second Expert Report noted an inverse association between alcoholic drinks and NHL, but did not draw any conclusion on its causality [3].

Several studies on the issue have been made available recently [4–10]. One of these was a large cohort investigation conducted in the UK, the Million Women Study, including 2320 women with NHL [4]. This reported a relative risk (RR) of NHL of 0.77 [95% confidence interval (CI) 0.62–0.94] for women consuming >2 drinks per day as compared with occasional drinkers (i.e. ≤2 drinks per week), with a significant inverse trend in risk for increasing levels of alcohol consumption (P = 0.001). Similar results emerged in another large prospective investigation of 1381 NHL cases, i.e., the USA National Institutes of Health-former American Association of Retired Persons (NIH-AARP) Study [11]. This found a RR of NHL of 0.77 (95% CI 0.59–1.00) for drinkers of >4 drinks per day as compared with non-drinkers. A few other investigations showed an inverse association between alcohol consumption and NHL [8, 12–15], while no consistent pattern of risk emerged in other epidemiological studies [6, 9, 10, 16, 17].

In order to provide a more precise quantification of the association between alcohol drinking and NHL risk, we conducted a systematic review and a meta-analysis of available data.
methods

identification of studies and data collection

We carried out a literature search, using PubMed, of all case–control and cohort studies published as original articles in English up to January 2011, using the terms ‘alcohol drinking’ or ‘alcoholic beverages’ and ‘lymphoma’, following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [18]. Potentially relevant papers were retrieved and assessed, and the reference lists in the articles were checked to identify additional publications of interest. When multiple reports were published on the same study, only the most informative one was considered. Eighty-three publications were identified, of which 37 were non-relevant, 12 were excluded because they did not report the odds ratio (OR) or RR and the corresponding 95% CI, or sufficient information to calculate them. Three articles were excluded since they reported estimates for Hodgkin lymphoma (HL) only, and two for HL and NHL combined. Thus, the present analyses were based on 29 studies: 21 case–control [5, 8, 13–17, 19–32] and 8 cohort [4, 6, 7, 9–12, 33] studies.

For each study, we extracted information on study design, country, sex, NHL subtypes considered, number of subjects (cases, controls, or cohort size), type of controls and period of enrolment for case–control studies, duration of follow-up for cohort studies, RR estimates and the corresponding CIs, adjustment variables, and, when available, the number of cases and non-cases or person-years (PY) for each category of alcohol consumption.

statistical analysis

The measure of interest was the RR, estimated by the OR in case–control and by the hazard ratio in cohort studies.

We used grams of alcohol per day as standard measurement unit, defining 1 drink as 12.5 g of alcohol. The dose associated to each RR estimate was computed as the midpoint of each exposure category, and, for the open-ended upper category, as 1.2 times its lower bound [34]. When possible, we chose non-drinkers as the reference category; however, in several studies, occasional drinkers were included in the reference category. Furthermore, a few studies chose moderate drinkers as the reference category. In order to estimate RRs using non-drinkers or occasional drinkers as reference, whenever available, we used the floating standard error [35, 36]. Otherwise, we estimated the covariance matrix using the method proposed by Greenland & Longnecker [37]. We considered three levels of alcohol consumption: light drinkers of ≤1 drink per day, moderate drinkers of >1 to <4 drinks per day, and heavy drinkers of ≥4 drinks per day. If in a study more than one exposure category fell into the same level, we combined the corresponding estimates using the method proposed by

---

**Figure 1.** Summary RRs of alcohol drinking (drinkers vs non-drinkers) and NHL. CI, confidence interval; M, men; M + W, men and women considered together; NHL, non-Hodgkin lymphoma; PY, person-years; RR, relative risk; W, women.
Hamling et al. [38], taking into account the correlation between estimates.

We generated forest plots for alcohol drinkers versus non-drinkers and for levels of alcohol consumption. We also calculated summary RRs of alcohol drinking in strata of selected covariates. All the estimates were derived using random-effects models [39]. We assessed the heterogeneity among studies using the $\chi^2$ test [39], defining a significant heterogeneity as a $P$ value <0.10, and evaluated the inconsistency using the $I^2$ statistic [40].

We carried out a dose–response analysis using a meta-regression model in a non-linear dose–response relationship framework, choosing the best-fitting two-term fractional-polynomial model [41].

To evaluate publication bias, we used the contour-enhanced funnel plot [42] and the Egger’s test for funnel plot asymmetry [43].

results

The main characteristics of the 29 studies [4–17, 19–33] included in the meta-analysis are given in supplementary Table S1 (available at Annals of Oncology online). A total of 18 759 NHL cases were included.

Figure 1 shows the summary RRs for drinkers versus non-drinkers. The overall RR was 0.85 (95% CI 0.79–0.91). The corresponding estimates were 0.80 (95% CI 0.74–0.87) for case–control and 0.96 (95% CI 0.88–1.04) for cohort studies ($P$ for heterogeneity between case–control and cohort estimates = 0.001).

Figure 2 gives the forest plots for light, moderate, and heavy alcohol drinking. The overall RRs were 0.88 (95% CI 0.81–0.96) for light, 0.87 (95% CI 0.79–0.95) for moderate, and 0.84 (95% CI 0.70–1.00) for heavy alcohol drinking, based on 23, 21, and 7 estimates, respectively. The corresponding estimates were 0.79, 0.85, and 0.92 among case–control, and 1.00, 0.89, and 0.79 among cohort studies.

Figure 3 shows the dose–response analysis, giving the RR function and the corresponding 95% CI for the best-fitting relationship between alcohol consumption and NHL risk [i.e. $\ln(\text{RR}) = \text{dose} + \text{dose} \times \ln(\text{dose})$]. This function estimated RRs of 0.91 (95% CI 0.87–0.94) for 10, 0.85 (95% CI 0.80–0.90) for 25, 0.80 (95% CI 0.74–0.87) for 50, 0.80 (95% CI 0.70–0.91)

![Figure 2. Summary RRs of NHL and light (≤1 drink per day) (A), moderate (>1 to <4 drinks per day) (B), and heavy (≥4 drinks per day) (C) alcohol drinking. CI, confidence interval; M, men; M + W, men and women considered together; NHL, non-Hodgkin lymphoma; PY, person-years; RR, relative risk; W, women.](image-url)
for 75, and 0.81 (95% CI 0.66–1.00) for 100 g of ethanol per day, respectively.

Table 1 considers the association between alcohol and NHL, in stratified analyses. No significant differences were found across strata of sex, type of controls (population-based versus hospital-based in case–control studies), and between the two main subtypes of NHL (i.e. T-cell versus B-cell NHL), or across the most common B-cell NHL subtypes (i.e. diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL)). The RRs were 0.78 in studies where former drinkers were considered together with never drinkers, 0.84 when combined with current drinkers, and 0.93 (for current versus never drinkers) when considered as a separate group in the analyses (P for heterogeneity = 0.50). In the latter analysis, the RR for former versus never drinkers was 1.06 (95% CI 0.84–1.35). The association was stronger in studies conducted in Asia (RR = 0.69) as compared with those from non-Asian countries (RR = 0.88, P for heterogeneity = 0.019).

Supplementary Figure S1 (available at *Annals of Oncology* online) shows the contour-enhanced funnel plot of studies on the association between alcohol drinking and NHL risk. The graph appears to be symmetrical, suggesting the absence of publication bias. Likewise, we found no asymmetry according to the Egger’s test (P = 0.121).

**discussion**

In the present meta-analysis, we found a 15% reduction of NHL risk among alcohol drinkers compared with non-drinkers, providing more precise quantitative evidence than previously available that alcohol drinking is inversely related to NHL.

Some caution in the interpretation of these findings is however needed. The inverse relationship observed could be partly attributable to a misclassification of drinkers among cases, since some of them could have stopped or decreased alcohol drinking as a consequence of symptoms, i.e. reverse...
causation. This is supported by the fact that cohort studies, which are less prone to reverse causation, reported a less strong association overall and with light alcohol consumption. For moderate and heavy drinking, however, there was no major difference in results across study design. Moreover, analyses by cancer subtype showed a significant reduction of DLBCL and FL risks, which are characterized by disease symptoms preceding the diagnosis, while no association was found for CLL/SLL, which are frequently diagnosed incidentally, in the absence of symptoms [44]. On the other hand, we did not find any significant heterogeneity across estimates from studies considering former drinkers together with never drinkers, together with current drinkers or as a separate group in the analyses. Thus, misclassification of former drinkers cannot totally explain the association observed. Similarly, findings were equal among hospital-based and population-based case-control studies, weighing against a role of selection bias in hospital-based (rather than in population-based) studies.

Under-reporting of alcohol consumption is also possible [45, 46]. However, studies investigating reproducibility and validity of self-reported alcohol drinking in various populations found satisfactory correlation coefficients, i.e. between 0.70 and 0.99 [6, 12, 22].

Compared with non-Asian countries, we observed a reduced risk in Asian population, which are characterized by a smaller prevalence of heavy drinking [47–49]. In fact, subjects with the ADH2 Arg and ALDH2 Lys polymorphisms (more common in Asia rather than in the rest of the world) cannot be heavy drinkers [47–49]. Since we identified only three studies from Asian countries, this finding needs further confirmation.

In this meta-analysis, there was a significant heterogeneity across estimates, with an $I^2$ for drinkers versus non-drinkers analysis of almost 60%. Therefore, in all the analyses, we used the random-effects models in order to account for heterogeneity among studies [39]. The contour-enhanced funnel plot and the Egger’s test for funnel plot asymmetry excluded the presence of publication bias, providing an indication of the robustness of our results. Finally, although, whenever possible, we used multivariate-adjusted risk estimates, a residual role of confounding cannot be ruled out.

Figure 2. (continued)
In fact, the causes of NHL remain largely undefined, recognized risk factors in the aetiology of NHL can explain only part of the cases [50], and satisfactory adjustment for all potential confounding factors is therefore impossible.

Data on alcohol drinking and different subtypes of NHL are sparse, and individual studies generally had low statistical power to address any association. Thus, a major strength of this investigation was the opportunity to resume the available evidence for several NHL subtypes, by providing separate summary estimates. According to our findings, the relation between alcohol drinking and NHL does not show significant differences across various cancer subtypes, the RRs varying between 0.78 for T-cell NHL and 0.86 for B-cell NHL, with the possible exception of CLL/SLL that showed no material association with alcohol consumption (RR = 1.00).
The reason for an inverse relation between alcohol drinking and NHL risk is not clear. Alcohol could decrease the risk of NHL through its immunomodulatory effect, since light or moderate consumption may enhance the immune response, resulting in a more effective host defense \[51, 52\]. Moreover, the presence of antioxidants in some alcoholic beverages and the improvement of insulin sensitivity by alcohol could support the potential favourable role of alcohol in NHL aetiology.

In conclusion, available epidemiological evidence indicates a favourable effect of alcohol on NHL risk. However, the lack of a biological explanation for these findings indicates caution in their interpretation.

**acknowledgements**

The authors thank Ms I. Garimoldi for editorial assistance.

**funding**

Italian Association for Cancer Research (10068, MFAG 10258); Italian Foundation for Cancer Research (to IT).

**disclosure**

The authors have declared no conflicts of interest.

**references**