A meta-analysis on alcohol drinking and esophageal and gastric cardia adenocarcinoma risk

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Background: In order to provide a precise quantification of the association between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk, we conducted a meta-analysis of available data.

Patients and methods: We identified 20 case–control and 4 cohort studies, including a total of 5500 cases. We derived meta-analytic estimates using random-effects models, taking into account correlation between estimates, and we carried out a dose–risk analysis using nonlinear random-effects meta-regression models.

Results: The relative risk (RR) for drinkers versus nondrinkers was 0.96 [95% confidence interval (CI) 0.85–1.09] overall, 0.87 (95% CI 0.74–1.01) for esophageal adenocarcinoma and 0.89 (95% CI 0.76–1.03) for gastric cardia adenocarcinoma. Compared with nondrinkers, the pooled RRs were 0.86 for light (<1 drink per day), 0.90 for moderate (1 to <4 drinks per day), and 1.16 for heavy (≥4 drinks per day) alcohol drinking. The dose–risk model found a minimum at 25 g/day, and the curve was <1 up to 70 g/day.

Conclusions: This meta-analysis provides definite evidence of an absence of association between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk, even at higher doses of consumption.

Key words: alcohol drinking, dose–risk relation, esophageal and gastric cardia adenocarcinomas, meta-analysis, systematic review

introduction

Squamous-cell carcinoma and adenocarcinoma of the esophagus differ substantially in their patterns of incidence and etiology. While gastroesophageal reflux disease and high body mass index (BMI) are the main risk factors for esophageal adenocarcinoma, the main determinants of esophageal squamous-cell carcinoma in Europe and North America are tobacco smoking and alcohol drinking [1–4]. Tobacco smoking is also associated with adenocarcinoma of the esophagus, although the association is less strong than for esophageal squamous-cell carcinoma [5, 6]. Moreover, it is not clear whether alcohol has any effect at all on esophageal adenocarcinoma [1].

Similarly, gastric noncardia and gastric cardia adenocarcinomas appear to have a different etiology. Helicobacter pylori infection is the main cause of noncardia gastric cancer but not of cardia cancer. In fact, for gastric cardia as well as for esophageal adenocarcinoma, H. pylori infection appears to have, if anything, a favorable role [2, 7]. With reference to alcohol, in 2007, an International Agency for Research on Cancer (IARC) working group concluded that alcohol was related to esophageal cancer, and there were suggestions of the carcinogenicity of alcohol drinking on gastric cancer [8], although it was not clear whether alcohol exerted a different effect on different portions of the stomach, particularly on the cardia. Another IARC working group reached to the same conclusions in 2009 [9].

Giving the similar etiologic determinants [2, 10] and the anatomical proximity, which makes the distinction between the two cancer sites difficult, esophageal and gastric cardia adenocarcinomas are frequently considered together.

In order to provide a definite quantification of the association between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk, we conducted a systematic review and a meta-analysis of studies published up to October 2010.

materials and methods

identification of studies and data collection

We carried out a literature search of all case–control and cohort studies published as original articles in English up to October 2010, using PubMed...
Table 1. Case-control and cohort studies on the association between alcohol consumption and esophageal and gastric cardia adenocarcinoma risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sex</th>
<th>Cancer site</th>
<th>No. of cases</th>
<th>No. of controls/size of cohort</th>
<th>Type of controls</th>
<th>Period of enrolment/duration of follow-up</th>
<th>Variables adjusted for in the regression models</th>
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</thead>
<tbody>
<tr>
<td>Case-control</td>
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</tr>
<tr>
<td>Wu-Williams et al. (1990)a</td>
<td>United States</td>
<td>M</td>
<td>GC</td>
<td>58</td>
<td>137</td>
<td>PB</td>
<td>1975–1982</td>
<td>Age, race</td>
</tr>
<tr>
<td>Gao et al. (1994)*</td>
<td>China</td>
<td>M + W</td>
<td>E</td>
<td>51</td>
<td>1552</td>
<td>PB</td>
<td>1990–1993</td>
<td>Sex, age, education, birthplace, smoking, tea drinking, dietary factors</td>
</tr>
<tr>
<td>Inoue et al. (1994)</td>
<td>Japan</td>
<td>M + W, M, W</td>
<td>GC</td>
<td>123</td>
<td>668</td>
<td>HB</td>
<td>1988–1991</td>
<td>Sex, age, time of hospital visit</td>
</tr>
<tr>
<td>De Stefani et al. (1998)</td>
<td>Uruguay</td>
<td>M</td>
<td>GC</td>
<td>24</td>
<td>622</td>
<td>HB</td>
<td>1992–1996</td>
<td>Age, residence, urban/rural status, smoking duration, vegetable intake</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sex</td>
<td>Cancer site</td>
<td>No. of cases</td>
<td>No. of controls/size of cohort</td>
<td>Type of controls</td>
<td>Period of enrolment/duration of follow-up</td>
<td>Variables adjusted for in the regression models</td>
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<tr>
<td>Lagergren et al. (2000)</td>
<td>Sweden</td>
<td>M + W</td>
<td>E, GC</td>
<td>451</td>
<td>820</td>
<td>PB</td>
<td>1995–1997</td>
<td>Sex, age, education, smoking, BMI, reflux symptoms, fruit, vegetable and energy intake, physical activity</td>
</tr>
<tr>
<td>Zaridze et al. (2000)</td>
<td>Russia</td>
<td>M, W</td>
<td>GC</td>
<td>92</td>
<td>610</td>
<td>HB</td>
<td>1996–1997</td>
<td>Age, education, smoking (for men); age, education, energy (for women)</td>
</tr>
<tr>
<td>Wu et al. (2001)</td>
<td>United States</td>
<td>M + W</td>
<td>E, GC</td>
<td>499</td>
<td>1356</td>
<td>PB</td>
<td>1992–1997</td>
<td>Sex, age, race, birthplace, education, smoking</td>
</tr>
<tr>
<td>Hashibe et al. (2007)</td>
<td>Central and Eastern Europe (Romania, Russia, Czech Republic, Poland)</td>
<td>M + W</td>
<td>E</td>
<td>35</td>
<td>1114</td>
<td>HB</td>
<td>2000–2002</td>
<td>Sex, age, center, education, BMI, fruit and vegetable intake, smoking</td>
</tr>
<tr>
<td>Anderson et al. (2009)</td>
<td>Ireland</td>
<td>M + W</td>
<td>E</td>
<td>227</td>
<td>260</td>
<td>PB</td>
<td>2002–2004</td>
<td>Sex, age, smoking, urban/rural status, BMI, job type, education, energy, fruit and vegetable intake, <em>Helicobacter pylori</em> infection, nonsteroidal antiinflammatory drugs, gastroesophageal reflux, location (for cases only)</td>
</tr>
<tr>
<td>Pandeya et al. (2009)</td>
<td>Australia</td>
<td>M + W, M, W</td>
<td>E, GC</td>
<td>785</td>
<td>1574</td>
<td>PB</td>
<td>2002–2005</td>
<td>Sex, age, BMI, frequency of heartburn or acid reflux, education, frequency of aspirin use, smoking</td>
</tr>
<tr>
<td>Cohort Lindblad et al. (2005)</td>
<td>UK</td>
<td>M + W</td>
<td>E, GC</td>
<td>482</td>
<td>10 000</td>
<td>Nested</td>
<td>1994–2001</td>
<td>Sex, age, calendar year, history of gastroesophageal reflux, BMI, smoking</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Sex</td>
<td>Cancer site</td>
<td>No. of cases</td>
<td>No. of controls/size of cohort</td>
<td>Type of controls</td>
<td>Period of enrolment/duration of follow-up</td>
<td>Variables adjusted for in the regression models</td>
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<tr>
<td>Freedman et al. (2007)</td>
<td>United States</td>
<td>M + W</td>
<td>E, GC</td>
<td>393</td>
<td>474 606 (PR); 2 121 797 (PY)</td>
<td>–</td>
<td>1995/1996–2000 (average 4.6 years of follow-up; interquantile range: 4.5–4.8 years)</td>
<td>Sex, age, BMI, education, physical activity, vegetable, fruit and energy intake, smoking</td>
</tr>
<tr>
<td>Allen et al. (2009)</td>
<td>UK</td>
<td>W</td>
<td>E</td>
<td>226</td>
<td>1.3 million (PR); 9.2 million (PY)</td>
<td>–</td>
<td>Recruitment: 1996–2001; follow-up: average of 7.2 years</td>
<td>Age, residence, socioeconomic status, BMI, smoking, physical activity, use of oral contraceptives and hormone replacement therapy</td>
</tr>
<tr>
<td>Steeves et al. (2010)</td>
<td>Netherlands</td>
<td>M + W</td>
<td>E, GC</td>
<td>309</td>
<td>3962 (PR); 56 806 (PY)</td>
<td>–</td>
<td>1986–2002 (16.3 years of follow-up)</td>
<td>Sex, age, smoking, BMI, education, energy, fruit, vegetable and fish intake</td>
</tr>
</tbody>
</table>

aStudies reporting adjusted RR estimates without CIs.
bThe corresponding reference category was ≤15.8 g of ethanol per day.
cThe corresponding reference category was moderate drinkers (>0 to 13 g of ethanol per day).
dThe corresponding reference category was moderate drinkers (>0 to 20 g of ethanol per week).

BMI, body mass index; E, esophagus; E + GC, esophagus and gastric cardia considered together; GC, gastric cardia; HB, hospital-based; M, men; M + W, men and women considered together; Nested, nested case–control study; PB, population based; PR, persons at risk; PY, person-years; W, women.
with the MeSH terms ‘alcohol drinking’ or ‘alcoholic beverages’ and ‘stomach neoplasms’ or ‘esophageal neoplasms’, following the Meta-analysis Of Observational Studies in Epidemiology guidelines [11]. Three of the authors (FI, LS and IT) retrieved and assessed potentially relevant papers, and reviewed the reference list in the articles to identify additional publications of interest. When multiple reports were published on the same study, we considered in the meta-analysis only the most informative one. We identified 70 publications, of which 46 were excluded because they did not fulfill the inclusion criteria (i.e. studies not reporting the odds ratio (OR) or relative risk (RR) and the corresponding 95% confidence intervals (CIs) of esophageal and/or gastric cardia adenocarcinoma separately from other subsites of esophageal and gastric cancers or sufficient information to calculate them). Thus, the present analyses were based on 24 studies: 20 case–control [5, 12–30] and 4 cohort [31–34] studies (Table 1).

For each study, we extracted information on study design, country, number of subjects (cases, controls or cohort size), type of controls and period of enrollment for case–control studies, duration of follow-up for cohort studies, cancer site, sex distribution of the study population, variables adjusted for in the analysis, RR estimates and the corresponding CI and, when available, the number of cases and noncases or person-years for each category of alcohol consumption.

**statistical analyses**

The measure of interest was the RR (estimated by the OR in case–control and the hazard ratio (HR) in cohort studies). Whenever available, we used multivariate-adjusted risk estimates; otherwise, we utilized or computed the unadjusted RRs. When studies reported adjusted RR estimates without CIs, we computed the standard error (SE) using the SE from the unadjusted RR penalized by a factor of 1.5, as done in previous meta-analyses on alcohol drinking and oral/pharyngeal [35] and laryngeal [36] cancers.

Since different measurement units were used to express alcohol intake, we converted alcohol consumption levels into grams of ethanol per day. 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

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**Figure 1.** Summary relative risks (RRs) of alcohol drinking (drinkers versus nondrinkers) and esophageal and gastric cardia adenocarcinoma, overall (A) and by anatomic subsite (B). CI, confidence interval; E, esophagus; E + GC, esophagus and gastric cardia considered together; GC, gastric cardia; M, men; M + W, men and women considered together; Py, person-years; W, women.
its lower bound [37]. We defined one drink as 12.5 g of ethanol. When possible, we chose nondrinkers as the reference category. In several studies, however, occasional drinkers were included in the reference category. Some studies chose moderate drinkers as the reference category. In order to estimate RRs using non- or occasional drinkers as reference, whenever available, we used the floating SE [38, 39]; otherwise, we estimated the covariance matrix using the method proposed by Greenland and Longnecker [40]. Besides nondrinkers, we considered three exposure levels to alcohol: light as drinkers of £1 drink per day, moderate as drinkers of 1 to <4 drinks per day, and heavy as drinkers of ≥4 drinks per day. If in a study more than one exposure category fell into one of these three levels, we combined the corresponding estimates using the method proposed by Hamling et al. [41], taking into account the correlation between estimates.

We generated forest plots for alcohol drinkers versus nondrinkers, overall and by cancer subsite (esophageal versus gastric cardia adenocarcinoma). We also calculated the overall RR estimates of esophageal and gastric cardia adenocarcinoma for light, moderate and heavy alcohol drinking and the RRs for alcohol drinkers versus nondrinkers in strata of selected covariates. All the meta-analytic estimates were derived using random-effects models [42]. We assessed the heterogeneity among studies using the χ² test [42], defining a significant heterogeneity as P < 0.10, and quantified the inconsistency using the I-squared statistic [43].

We carried out a dose–response analysis using a random-effects meta-regression model in a nonlinear dose–response relationship framework, choosing the best-fitting two-term fractional-polynomial model [44].

We also carried out a publication bias analysis, through the contour-enhanced funnel plot [45], and the Egger’s test for funnel plot asymmetry [46].

results

The main characteristics of the 24 studies [5, 12–34] are given in Table 1. Four studies were conducted in Asia, one in Australia, eight in Europe, one in Russia, nine in the United States, and one in Uruguay. A total of 5500 esophageal and/or gastric cardia adenocarcinoma cases were included.

Figure 1 shows the RRs of alcohol drinking (drinkers versus nondrinkers) and esophageal and gastric cardia adenocarcinoma, overall and by anatomic subsite. The summary RR was 0.96 (95% CI 0.85–1.09). The corresponding estimates were 0.99 (95% CI 0.83–1.17) for case–control and [42].
0.94 (95% CI 0.83–1.08) for cohort studies (P for heterogeneity = 0.639). The summary RRs were 0.87 (95% CI 0.74–1.01) for esophageal and 0.89 (95% CI 0.76–1.03) for gastric cardia adenocarcinoma (P for heterogeneity = 0.838), based on 13 and 14 studies, respectively.

Figure 2 gives the forest plots for light, moderate and heavy alcohol drinking. The overall RRs were 0.86 (95% CI 0.75–0.99) for light, 0.90 (95% CI 0.73–1.10) for moderate, and 1.16 (95% CI 0.92–1.46) for heavy alcohol drinking, based on 15, 16 and 13 studies, respectively. The RRs for heavy alcohol drinking were 1.10 (95% CI 0.80–1.50) for esophageal and 0.98 (95% CI 0.78–1.23) for gastric cardia adenocarcinoma (P for heterogeneity = 0.560), based on seven and eight studies, respectively (data not shown).

Table 2 considers the association between alcohol and esophageal and gastric cardia adenocarcinoma risk in stratified analyses. No significant differences were found between men and women or between studies with and without adjustment for smoking habit, BMI, fruit and vegetable consumption and gastroesophageal reflux, although the summary RRs derived from the adjusted estimates tended to be lower than the unadjusted ones.

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 esophageal and gastric cardia adenocarcinoma risk (i.e. ln(RR) = dose + dose × ln(dose)). This function shows no significantly increased risk at any level of alcohol intakes, with a minimum at 25 g/day, and the curve was <1 up to 70 g/day. None of the estimates for subsequent doses, however, were significant.

Figure 4 provides the contour-enhanced funnel plot of studies on the association between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk. The graph appears to be symmetrical, suggesting the absence of a publication bias. Likewise, we found no asymmetry according to the Egger’s test (P = 0.202).

discussion

A relation between alcohol drinking and esophageal and gastric cardia adenocarcinoma risk is biologically plausible, since animal studies have shown that alcohol increases
gastroesophageal reflux by causing relaxation of the lower esophageal sphincter [47]. However, in the present meta-analysis, we did not find any significant association. Thus, recent changes in the incidence and distribution of adenocarcinoma of the esophagus and gastric cardia observed in several developed countries [1, 4, 10, 48–51] cannot be explained by changes in terms of exposure to alcohol consumption.

No association was found even when adenocarcinomas of the esophagus and of the gastric cardia were considered separately. In a companion meta-analysis on alcohol consumption and gastric cancer risk, we found a moderate positive association, which was, however, confined to noncardia gastric cancers [52].

We did not find a significant association with alcohol drinking also for high levels of consumption, both considering heavy alcohol drinkers separately from the other categories of consumption and performing a dose–response analysis based on the best-fitting two-term fractional-polynomial model. The pooled RR for light alcohol drinking was below unity among both case–control and cohort studies, and the dose–risk analysis also showed a minimum ~25 g/day. This may reflect more favorable dietary patterns of moderate alcohol drinkers compared with either non- or heavy drinkers in several populations [53–55]. In order to avoid confounding by other major risk factors, including gastroesophageal reflux, overweight and obesity, smoking and low fruit and vegetable consumption, whenever possible, we used multivariate-adjusted risk estimates. Furthermore, the pooled RRs for drinkers versus nondrinkers derived from estimates adjusted by these factors were below unity (~0.8–0.9), while the pooled RRs derived from unadjusted ones were ~1, suggesting that residual confounding by smoking, BMI, fruit and vegetable consumption and gastroesophageal reflux did not modify the association with alcohol.

Compared with meta-analyses of randomized clinical trials, those based on observational studies are more prone to biases and other sources of heterogeneity [56]. The use of the random-effects model took into account heterogeneity among studies in the estimation of the pooled RR [42]. Furthermore, most data derived from retrospective exposure assessment in case–control studies and were therefore subject to biases and limitations. However, results from cohort studies were similar to those from case–control ones, and, if anything, provided a more definite evidence of a lack of association between
Figure 2. (Continued)

Figure 3. Relative risk function and the corresponding 95% confidence interval, describing the best-fitting dose–response relationship between alcohol consumption and esophageal and gastric cardia adenocarcinoma risk.
alcohol drinking and esophageal and gastric cardia adenocarcinoma risk. Other limitations of our meta-analysis include possible underreporting of alcohol consumption in several studies [57, 58]. However, in the presence of a positive dose-dependent association and of a systematic underreporting by cases (differential underreporting) of alcohol consumption, this would lead to an overestimation of the RR at lower doses and can be excluded giving the negative association emerged for light alcohol drinking. Finally, the contour-enhanced funnel plot and the Egger’s test for funnel plot asymmetry did not show any evidence of publication bias, providing further indication of the robustness of our results.

In conclusion, the present meta-analysis provides a clear evidence of a lack of association between alcohol consumption and esophageal and gastric cardia adenocarcinoma risk, even at higher doses of consumption. An open question for future research is whether an association exists considering different alcoholic beverages separately.

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disclosure
The authors declare no conflict of interest.

references


