META-ANALYSIS

Dose-specific Meta-Analysis and Sensitivity Analysis of the Relation between Alcohol Consumption and Lung Cancer Risk

Jeffrey E. Korte, Paul Brennan, S. Jane Henley, and Paolo Boffetta

Alcohol drinking increases the risk of several types of cancer, but studies of the relation between alcohol and lung cancer risk are complicated by smoking. The authors carried out meta-analyses for four study designs and conducted sensitivity analyses to assess the results. Pooled smoking-unadjusted relative risks (RRs) for brewery workers and alcoholics were 1.17 (95% confidence interval (CI): 0.99, 1.39) and 1.99 (95% CI: 1.66, 2.39), respectively, relative to population rates. For cohort and case-control studies, the authors conducted dose-specific meta-analyses for ethanol consumption of 1–499, 500–999, 1,000–1,999, and ≥2,000 g/month, relative to nondrinking. Smoking-adjusted RRs for ascending dose groups in cohort studies were 0.98 (95% CI: 0.79, 1.21), 0.92 (95% CI: 0.81, 1.04), 1.04 (95% CI: 0.88, 1.22), and 1.53 (95% CI: 1.04, 2.25), respectively. Smoking-adjusted odds ratios for ascending groups in case-control studies were 0.63 (95% CI: 0.51, 0.78), 1.30 (95% CI: 0.98, 1.70), 1.13 (95% CI: 0.46, 2.75), and 1.86 (95% CI: 1.39, 2.49), respectively. Elevated odds ratios were seen for hospital-based case-control studies but not for population-based case-control studies. Sensitivity analyses indicated that smoking explained the elevated RRs in studies of alcoholics and that strong misclassification of smoking status could produce an elevated smoking-adjusted RR in cohort and case-control studies. Overall, evidence for a smoking-adjusted association between alcohol and lung cancer risk is limited to very high consumption groups in cohort and hospital-based case-control studies. At lower levels, any associations observed appear to be explained by confounding. Am J Epidemiol 2002;155:496–506.

alcohol drinking; lung neoplasms; meta-analysis; smoking

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Abbreviations: CI, confidence interval; CPS, Cancer Prevention Study; RR, relative risk.

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Alcohol consumption is an established risk factor for cancers of the oral cavity, pharynx, larynx, esophagus, and liver (1). An association between alcohol drinking and lung cancer risk has also been reported. Studies of the relation between alcohol and lung cancer are difficult to interpret, however, because of the confounding effects of smoking. Cigarette smoking is a strong risk factor for lung cancer, and in many countries smoking is highly correlated with alcohol consumption. In several studies, investigators have found associations between alcohol and lung cancer after attempting to control for smoking (1–8). However, because of the strong relations between alcohol use and smoking and between smoking and lung cancer, it is possible that these results may be due to residual confounding by smoking.

The purpose of this study was to review quantitatively the epidemiologic literature on the relation between alcohol consumption and lung cancer risk. As an aid in interpretation of the results, we conducted a sensitivity analysis to assess the role that residual confounding by cigarette smoking could have played in producing the observed associations.

MATERIALS AND METHODS

Identification of studies

We conducted a comprehensive search for studies of the relation between alcohol drinking and lung cancer. In a primary search, we searched the MEDLINE database (US National Library of Medicine) using the keywords “alcohol” and “lung cancer.” We conducted secondary searches for additional studies of alcoholics and brewery workers, using the search terms [“alcoholic” or “brewery”] and [“lung” or “cancer” or “incidence” or “mortality”]. We searched for additional studies referenced in identified publications, review articles (2–8), and other relevant scientific publications (1, 9).

We included studies with an adequate estimate of relative risk (RR) between alcohol drinkers and nondrinkers and a measure of precision for the RR estimate (i.e., a standard error or confidence interval) or sufficient information...
for us to calculate such a measure. We included results for total alcohol consumption whenever possible. If results were only presented separately for different types of alcoholic beverages, we extracted the results corresponding to the type of alcohol most frequently consumed in the study population. In almost all cohort and case-control studies, investigators had obtained data only on frequency of current alcohol consumption rather than a cumulative estimate of consumption, or data on frequency of consumption in the more distant past. Where more than one set of results was presented, we chose results based on consumption frequency over as long a time span as possible. If more than one follow-up analysis had been published for the same population, we used the most recently published report. In some cases, we calculated a measure of RR and/or precision if the measure had not been published but was calculable from the data reported (e.g., number of lung cancer cases in different alcohol exposure groups and person-years of follow-up for each exposure group). Results of cohort studies were expressed as RRs, and results of case-control studies were expressed as odds ratios; for simplicity, however, we use “RR” to refer to both types of measures in this paper.

Data analysis

Epidemiologic studies of the relation between alcohol and lung cancer may be divided into three general types: case-control studies, population-based cohort studies with an internal reference group, and cohort studies of presumed excessive drinkers with an external reference group (3). We conducted separate meta-analyses for case-control and cohort studies, using only the results from the highest alcohol consumption group presented in each study. In addition, we conducted separate meta-analyses for studies of the two types of presumed excessive drinkers: brewing industry workers and alcoholics.

For cohort and case-control studies, we also conducted dose-specific meta-analyses with and without adjustment for smoking. In addition, because of the potential differences between hospital-based and population-based case-control studies in estimating etiologic relations involving alcohol and tobacco, we analyzed smoking-adjusted results separately for these two case-control study designs. We estimated total grams of ethanol consumed per month for each category presented in the results of each study, assuming 13 g of ethanol per bottle of beer (330 ml), glass of wine (150 ml), or shot of liquor (40 ml) (10). Based on the consumption distribution in all cohort and case-control studies, we defined four ethanol consumption groups: 1–499, 500–999, 1,000–1,999, and ≥2,000 g/month. At each consumption level, alcohol drinkers were compared with nondrinkers. If more than one dose-specific result from a single study fell within one of our four categories, we used a weighted average (with appropriate standard error) in the dose-specific meta-analysis. One cohort study (11) and three case-control studies (12–14) could not be included in dose-specific analyses, because we were unable to estimate quantitative alcohol consumption levels.

In addition to the meta-analysis of published cohort studies, we conducted new analyses of data from two large cohorts previously assembled by the American Cancer Society, the Cancer Prevention Study I (CPS-I) and Cancer Prevention Study II (CPS-II) cohorts. The CPS studies have been described previously (15, 16).

Simulations of misclassification and control for confounding

We conducted simulations of cohort studies, with various levels of tobacco and alcohol misclassification, to evaluate the possible effects of misclassification on the pooled results from cohort studies. In these simulations, we constructed hypothetical cohort studies of 100,000 people, with a smoking-adjusted RR of 1.0 for the relation between alcohol consumption and lung cancer. Estimates of the cumulative risk of lung cancer (17), prevalences of smoking and drinking (18–25), and the RR for smoking and lung cancer (26–30) were taken from the literature. Characteristics of the first simulated cohort were: risk of lung cancer death during follow-up = 7 percent; population prevalence of smoking = 40 percent; RR for smoking and lung cancer = 15; and prevalence of alcohol drinking = 75 percent among smokers and 40 percent among nonsmokers. Characteristics of the second simulated cohort were: risk of lung cancer death during follow-up = 7 percent; prevalence of heavy smoking = 10 percent and prevalence of light smoking = 30 percent; RR for smoking and lung cancer = 20 for heavy smokers and 10 for light smokers; and prevalences of alcohol drinking among smokers as follows: 50 percent heavy drinkers and 40 percent light drinkers among heavy smokers, 30 percent heavy drinkers and 30 percent light drinkers among light smokers, and 10 percent heavy drinkers and 30 percent light drinkers among nonsmokers.

Using these simulated cohorts, we conducted two types of sensitivity analyses to assess the effect of misclassification on the smoking-adjusted RR for alcohol and lung cancer. In one simulation, drinkers were misclassified as nondrinkers and smokers as nonsmokers. In the second simulation, heavy drinkers were misclassified as light drinkers and heavy smokers as light smokers. We assumed misclassification to be independent of outcome, reflecting the prospective study design. Additionally, we assumed alcohol misclassification to be independent of smoking status and vice versa.

In the published cohort studies of presumed excessive drinkers, no direct adjustment for smoking was possible when comparing lung cancer rates among alcoholics or brewery workers with rates in the general population. We simulated an adjustment for smoking to evaluate its possible role as a confounder in studies of alcoholics. In these simulations, estimates of the prevalence of smoking among alcoholics and in the general population were taken from published surveys (18, 31–39), and estimates of the relation between smoking and lung cancer were taken from large cohort studies (26–30). All Mantel-Haenszel estimates of adjusted RR were calculated on the basis of person-years of exposure in the simulated cohorts.
Publication bias

For cohort studies, case-control studies, studies of alcoholics, and studies of brewery workers, we evaluated publication bias through methods developed by Beggs and Mazumdar (40) and Egger et al. (41). With each of these methods, we combined visual examinations of graphic plots with quantitative assessments of publication bias tests.

Statistical methods

Stata statistical software (Stata Corporation, College Station, Texas) was used for all meta-analyses and assessments of publication bias. We used a random-effects model for each meta-analysis. We did not attempt to weight studies by quality criteria. SAS statistical software (SAS Institute, Inc., Cary, North Carolina) was used for all simulations of misclassification and confounding.

RESULTS

Details on the studies included in this meta-analysis are summarized in table 1 (11–14, 42-75). Overall pooled results based on the highest consumption category from each study are presented in table 2. Studies of alcoholics showed a fairly substantial increase in lung cancer risk in relation to general population rates, with a pooled RR of 1.99 (95 percent confidence interval (CI): 1.66, 2.39). Studies of brewery industry workers, however, showed only a very slight excess risk of lung cancer, with a pooled RR of 1.17 (95 percent CI: 0.99, 1.39). For cohort studies, the pooled unadjusted RR in relation to nondrinkers was 1.42 (95 percent CI: 1.16, 1.73), while the pooled smoking-adjusted RR was attenuated to 1.19 (95 percent CI: 1.11, 1.29). For case-control studies, the pooled unadjusted odds ratio was 2.18 (95 percent CI: 1.68, 2.84), while the pooled smoking-adjusted odds ratio was 1.39 (95 percent CI: 1.06, 1.83).

Dose-specific results

In table 2, we also present dose-specific results from cohort and case-control studies, unadjusted and adjusted for cigarette smoking. For ease of comparison within each dose level, we include only studies that provided both unadjusted and adjusted results. Results based on all available studies were very similar (data not shown). In meta-analyses of unadjusted results from cohort studies, the RR for lung cancer in comparison with nondrinkers was close to 1.0 for low and intermediate ethanol consumption groups, but it increased to 2.10 (95 percent CI: 1.45, 3.05) for consumption in the highest category (≥2,000 g/month), based on the presence of only one study (67). Similarly, results adjusted for smoking showed an increased risk only in the highest category, with an RR of 1.53 (95 percent CI: 1.04, 2.25). Smoking-adjusted results in the highest consumption category were similar when we included two other cohort studies that did not present unadjusted results (56, 62); the pooled RR was 1.63 (95 percent CI: 1.20, 2.20).

For case-control studies (table 2), unadjusted results showed a notable increase in lung cancer risk beginning at lower levels of alcohol intake than in cohort studies. Alcohol drinkers in the lowest consumption category had no increased risk relative to nondrinkers, but the odds ratio steadily increased in higher consumption categories. The odds ratio for the highest category (≥2,000 g/month) was 3.57 (95 percent CI: 2.62, 4.88), based on one study (73). After adjustment for smoking, these results were attenuated and showed a substantial risk increase only in the highest category, with an odds ratio of 1.86 (95 percent CI: 1.39, 2.49).

Smoking-adjusted results in the highest consumption category were similar when we included another case-control study that did not present unadjusted results (74); the pooled odds ratio was 1.82 (95 percent CI: 1.41, 2.35). However, these two studies were both hospital-based. Because of the potential differences between hospital-based and population-based case-control studies in estimating etiologic relations involving alcohol and tobacco, we analyzed smoking-adjusted results separately for each study design (table 3). Overall, hospital-based case-control studies showed a smooth dose-response relation. Population-based case-control studies provided no evidence for a relation between alcohol consumption and lung cancer; however, only one study was available in the third consumption category, and none were available in the highest category.

In table 4, we present previously unpublished results from the CPS-I and CPS-II cohort studies and updated pooled RRs that include these results with those of the other cohort studies identified for this meta-analysis. Overall, smoking-adjusted results from CPS-I provided support for an association between alcohol consumption and lung cancer, while results from CPS-II did not support such an association. In the highest consumption category (≥2,000 g/month), the smoking-adjusted RRs in CPS-I were 1.40 (95 percent CI: 1.21, 1.62) and 2.34 (95 percent CI: 1.39, 3.93) for men and women, respectively, in relation to nondrinkers. Corresponding RRs in CPS-II were 1.20 (95 percent CI: 1.03, 1.39) and 1.12 (95 percent CI: 0.81, 1.54). In the updated meta-analysis (table 4), the unadjusted associations were somewhat weaker than the results shown in table 2, ranging up to 2.64 (95 percent CI: 2.21, 3.15) in the highest alcohol exposure group. However, the updated pooled smoking-adjusted association was slightly weaker in the highest alcohol consumption category, with an RR of 1.35 (95 percent CI: 1.16, 1.58).

Simulations of control for confounding

Neither the studies of alcoholics nor the studies of brewery workers were adjusted for differences in smoking habits between the study populations and the comparison populations, although in one study of alcoholics (48), no lung cancer excess was observed relative to a second reference population thought to have more similar smoking habits. We simulated control for smoking using our pooled smoking-unadjusted RR of 1.99 from studies of alcoholics and employing various assumptions for the prevalence of smoking in the general population, the prevalence of smoking among alcoholics, and...
### TABLE 1. Summary of data from studies of alcohol consumption and lung cancer risk identified for meta-analysis

<table>
<thead>
<tr>
<th>Type of study, author(s), and year (ref.)</th>
<th>No. of lung cancer cases</th>
<th>No. in cohort or no. of controls</th>
<th>Highest consumption category (estimated grams of ethanol per month)</th>
<th>Data adjusted for smoking?</th>
<th>Risk ratio*</th>
<th>95% confidence interval</th>
<th>Source of controls</th>
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<td>19</td>
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<td>1.44</td>
<td>0.87, 2.25</td>
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<td>Pell and D’Alonzo, 1973 (43)</td>
<td>5</td>
<td>992</td>
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<td>2.56</td>
<td>0.50, 13.17</td>
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<td>Hakulinen et al., 1974 (44)</td>
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<tr>
<td>Chronic alcoholics</td>
<td>33</td>
<td>&gt;4,370†</td>
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<td>1.13, 2.30</td>
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<td>Alcohol misusers</td>
<td>200</td>
<td>&gt;68,333‡</td>
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<td>Prior, 1988 (49)</td>
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<td>Adami et al., 1992 (50)</td>
<td>3</td>
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<td>2.7</td>
<td>0.6, 8.0</td>
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<td>Tonnesen et al., 1994 (51)</td>
<td>485</td>
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<td>2.3, 2.8</td>
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<td>Sigvardsson et al., 1996 (52)</td>
<td>139</td>
<td>15,508</td>
<td>No</td>
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<td>5.0</td>
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<td>Dean et al., 1979 (53)</td>
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<td>1,626§</td>
<td>No</td>
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<td>0.80, 1.20</td>
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<td>2,600</td>
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<td>10,602</td>
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<td>3,415</td>
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<td>0.77, 1.30</td>
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<td>Yong et al., 1997 (64)</td>
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<td>150</td>
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<td>Bandera et al., 1997 (65)</td>
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<td>Woodson et al., 1999 (66)</td>
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<td>27,111</td>
<td>1,260</td>
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<td>Prescott et al., 1999 (67)</td>
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<td>194</td>
<td>13,053</td>
<td>2,652</td>
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<td>Bradshaw and Schonlaid, 1969 (12)</td>
<td>45</td>
<td>341</td>
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<td>Williams and Horm, 1977 (13)</td>
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<td>1.05, 1.56</td>
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<td>Mothers</td>
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<td>66</td>
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<td>936</td>
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<td>585</td>
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<td>1.9</td>
<td>0.96, 3.90</td>
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<td>564</td>
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<td>Yes#</td>
<td>1.47</td>
<td>1.07, 2.01</td>
<td>Population</td>
</tr>
<tr>
<td>De Stefani et al., 1993 (73)</td>
<td>327</td>
<td>350</td>
<td>5,616</td>
<td>Yes#</td>
<td>2.2</td>
<td>1.3, 3.0</td>
<td>Hospital</td>
</tr>
<tr>
<td>Dosemeci et al., 1997 (74)</td>
<td>1,210</td>
<td>829</td>
<td>2,509</td>
<td>Yes#</td>
<td>1.7</td>
<td>1.0, 2.9</td>
<td>Hospital</td>
</tr>
<tr>
<td>Carpenter et al., 1998 (75)</td>
<td>261</td>
<td>615</td>
<td>1,560</td>
<td>Yes#</td>
<td>0.68</td>
<td>0.33, 1.41</td>
<td>Population</td>
</tr>
</tbody>
</table>

* Risk ratio in relation to general population rates (studies of alcoholics or brewery workers) or nondrinkers (cohort or case-control studies).
† Mean annual number of people listed in the chronic alcoholics registry from 1967 to 1970 = 4,370.
‡ Mean annual number of people listed in the alcohol misusers registry from 1944 to 1959 = 205,000; one third of 1968 Finnish lung cancer registry entries were checked against alcohol misusers registry.
¶ NA, not available.
# Smoking-adjusted results (odds ratio = 1.00 for men and 0.70 for women) could not be included in the meta-analysis because no estimate of variance was provided.
the strength of the association between smoking and lung cancer. Assuming an RR of 1.5 for the relation between smoking and lung cancer and a 70 percent prevalence of smoking among alcoholics, the simulated Mantel-Haenszel smoking-adjusted RRs were 0.96, 1.22, and 1.47 under the assumptions of 30 percent, 40 percent, and 50 percent prevalences of smoking in the general population, respectively. Assuming an 80 percent smoking prevalence among alcoholics, the simulated smoking-adjusted RRs were 0.85, 1.08, and 1.30, respectively. Finally, assuming a 90 percent smoking prevalence among alcoholics, the simulated smoking-adjusted RRs were 0.76, 0.97, and 1.17, respectively. Most estimates of smoking prevalence among alcoholics are 80–90 percent or higher, while estimates in the general population are below 50 percent. Under these assumptions, our simulated smoking-adjusted RRs showed clearly that uncontrolled confounding by smoking may be responsible for the observed excess of lung cancer among alcoholics.

<table>
<thead>
<tr>
<th>Study design</th>
<th>Risk estimate</th>
<th>Adjusted for smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted for smoking</td>
<td>Adjusted for smoking</td>
</tr>
<tr>
<td></td>
<td>RR*,†</td>
<td>95% CI*</td>
</tr>
<tr>
<td>Studies of alcoholics</td>
<td>1.99</td>
<td>1.66, 2.39</td>
</tr>
<tr>
<td>Studies of brewery workers</td>
<td>1.17</td>
<td>0.99, 1.39</td>
</tr>
</tbody>
</table>

| Cohort studies                |               |                     |
| Ethanol consumption (g/month)§|               |                     |
| Nondrinker                    | 1.00          | 1.00                |
| 1–499                         | 1.08          | 0.98, 1.21          | 5      |
| 500–999                       | 0.93          | 0.92, 1.04          | 3      |
| 1,000–1,999                   | 1.14          | 1.04, 1.22          | 3      |
| ≥2,000                        | 2.10          | 1.53, 2.25          | 1      |
| Overall†‡                     | 1.42          | 1.19, 1.29          | 11     |

| Case-control studies          |               |                     |
| Ethanol consumption (g/month)§|               |                     |
| Nondrinker                    | 1.00          | 1.00                |
| 1–499                         | 1.07          | 0.63, 0.88          | 3      |
| 500–999                       | 1.96          | 0.98, 1.70          | 3      |
| 1,000–1,999                   | 2.52          | 0.46, 2.75          | 2      |
| ≥2,000                        | 3.57          | 1.39, 2.49          | 1      |
| Overall†‡                     | 2.18          | 1.39, 1.83          | 7      |

* RR, risk ratio; CI, confidence interval.
† Risk ratio in relation to general population rates (studies of alcoholics or brewery workers) or nondrinkers (cohort or case-control studies).
‡ Number of studies contributing to the pooled estimate.
§ Dose-specific results using only studies with both adjusted and unadjusted results; the same studies are shown at each dose level.
¶ Overall results using all available studies; based on the highest alcohol consumption group from each study.

The results of the meta-analysis of alcohol consumption and lung cancer risk are presented in Table 2. The table shows the risk estimates for different levels of alcohol consumption, both unadjusted and adjusted for smoking. The unadjusted risk estimates range from 1.00 to 1.99, while the adjusted risk estimates range from 0.96 to 1.47. The number of studies contributing to the pooled estimate ranges from 3 to 12.

<table>
<thead>
<tr>
<th>Alcohol consumption</th>
<th>Population controls</th>
<th>Hospital controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR†,‡ 95% CI</td>
<td>No. of studies§</td>
</tr>
<tr>
<td>Nondrinker</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1–499</td>
<td>0.60  0.40, 0.88</td>
<td>3</td>
</tr>
<tr>
<td>500–999</td>
<td>0.96  0.52, 1.81</td>
<td>4</td>
</tr>
<tr>
<td>1,000–1,999</td>
<td>0.68  0.33, 1.40</td>
<td>1</td>
</tr>
<tr>
<td>≥2,000</td>
<td>1.09  0.63, 1.88</td>
<td>4</td>
</tr>
<tr>
<td>Overall†‡</td>
<td>1.09  0.63, 1.88</td>
<td>4</td>
</tr>
</tbody>
</table>

* Based on all available studies. Data were adjusted for cigarette smoking.
† OR, odds ratio; CI, confidence interval.
‡ Odds ratio for alcohol consumption and lung cancer risk in relation to nondrinkers.
§ Number of studies contributing to the pooled estimate.
¶ Based on the highest alcohol consumption group from each study.
Simulations of misclassification

To conduct a sensitivity analysis of the pooled smoking-adjusted RR for cohort studies, we simulated cohorts of 100,000 subjects with a smoking-adjusted RR of 1.0 for the relation between alcohol consumption and lung cancer, as previously described. The effects of misclassification of drinkers as nondrinkers and of smokers as nonsmokers were simultaneously evaluated. To illustrate the results, we created a table (Table 5) that summarizes the effects of misclassification on the simulated unadjusted RR and the simulated smoking-adjusted RR. With no misclassification, the simulated unadjusted RR comparing alcohol drinkers with nondrinkers was 2.10 (95% CI: 2.00, 2.21), demonstrating the confounding effect of smoking. Overall, increasing misclassification of drinkers as nondrinkers resulted in attenuation of the simulated unadjusted RR, and in some cases attenuation of the simulated smoking-adjusted RR. However, an inflation of the simulated smoking-adjusted RR occurred when misclassification of smokers as nonsmokers was higher than misclassification of drinkers as nondrinkers. Under the condition of no drinking misclassification and 10% smoking misclassification, the simulated smoking-adjusted RR was 1.15 (95% CI: 1.10, 1.20)—comparable to the pooled smoking-adjusted RR of 1.19 observed in our overall meta-analysis (Table 2). With no drinking misclassification and 20% smoking misclassification, the simulated adjusted RR rose to 1.29 (95% CI: 1.23, 1.35), and with no drinking misclassification and 30% smoking misclassification, the simulated adjusted RR rose to 1.39 (95% CI: 1.33, 1.45). These results indicate that under certain conditions of ≥10% misclassification from “smoker” to “nonsmoker” but very low drinking misclassification, our pooled smoking-adjusted results could be observed despite a true adjusted RR of 1.0.

Studies of nonsmokers may be the most valid design for assessing the relation between alcohol and lung cancer. However, the bias was much weaker than in the first part of our cohort simulations (Table 5). With 20% smoking misclassification (from “heavy smoker” to “light smoker”) and no drinking misclassification, the simulated smoking-adjusted RR for light drinkers and heavy drinkers was 1.07 (95% CI: 1.01, 1.14) and 1.10 (95% CI: 1.04, 1.17), respectively.

### Table 4. Results of analyses incorporating previously unpublished data on alcohol consumption and lung cancer risk from the Cancer Prevention Study I and II cohorts

<table>
<thead>
<tr>
<th>Ethanol consumption (g/month)</th>
<th>Cancer Prevention Study I</th>
<th>Cancer Prevention Study II</th>
<th>Updated meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 379,575)</td>
<td>Women (n = 489,741)</td>
<td>Men (n = 226,871)</td>
</tr>
<tr>
<td>Unadjusted for smoking</td>
<td>RR†, 95% CI</td>
<td>RR†, 95% CI</td>
<td>RR†, 95% CI</td>
</tr>
<tr>
<td>Nondrinker</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1–499</td>
<td>1.08</td>
<td>1.06, 1.32</td>
<td>1.00</td>
</tr>
<tr>
<td>500–999</td>
<td>1.38</td>
<td>1.41, 1.84</td>
<td>1.00</td>
</tr>
<tr>
<td>1,000–1,999</td>
<td>1.78</td>
<td>1.56, 2.02</td>
<td>1.00</td>
</tr>
<tr>
<td>≥2,000</td>
<td>2.25</td>
<td>2.15, 2.89</td>
<td>1.00</td>
</tr>
<tr>
<td>Adjusted for smoking</td>
<td>RR‡, 95% CI</td>
<td>RR‡, 95% CI</td>
<td>RR‡, 95% CI</td>
</tr>
<tr>
<td>Nondrinker</td>
<td>1.00</td>
<td>0.84, 0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>1–499</td>
<td>0.91</td>
<td>0.79, 0.99</td>
<td>1.00</td>
</tr>
<tr>
<td>500–999</td>
<td>1.03</td>
<td>0.88, 1.15</td>
<td>1.00</td>
</tr>
<tr>
<td>1,000–1,999</td>
<td>1.20</td>
<td>0.86, 1.11</td>
<td>1.00</td>
</tr>
<tr>
<td>≥2,000</td>
<td>1.49</td>
<td>1.03, 1.39</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Cancer Prevention Study I and Cancer Prevention Study II were conducted by the American Cancer Society (15, 16).
† RR, risk ratio; CI, confidence interval.
‡ Risk ratio in relation to nondrinkers.
§ Pooled results as shown in table 2, updated to include previously unpublished results from Cancer Prevention Study I and Cancer Prevention Study II.

Although studies of nonsmokers are unlikely to include alcoholics relative to the general population. These results are almost identical to the assumption of only a 10-fold association between smoking and lung cancer (data not shown).
heavy drinkers. We identified four case-control studies with information on nonsmokers and conducted new analyses of the CPS-I and CPS-II data. Results from analyses of these six studies of nonsmokers (table 7) provided inconsistent evidence of a small association between alcohol and lung cancer. Two case-control studies showed no differences in alcohol consumption between cases and controls: In one (76), the highest consumption category was approximately ≥1,000 g of ethanol per month, but in the other (77), no quantitative information on levels of alcohol consumption was presented. Another small study (78) found an elevated odds ratio of 1.85 (95 percent CI: 0.93, 3.70) among subjects consuming at least 52 g of ethanol per month relative to nondrinkers. In another study (79), an odds ratio of 2.22

| TABLE 5. Results of first simulation of misclassification in cohort studies of alcohol consumption and lung cancer risk* |
|---------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Misclassification (%) | Simulated risk ratio† |  |
| From smoker to nonsmoker | From drinker to nondrinker | Crude RR‡ 95% CI‡ | Smoking-adjusted RR§ 95% CI |
| 0 | 0 | 2.10 2.00, 2.21 1.00 0.95, 1.05 |
| 0 | 10 | 1.88 1.79, 1.97 1.00 0.95, 1.05 |
| 0 | 20 | 1.73 1.65, 1.81 1.00 0.96, 1.05 |
| 0 | 30 | 1.62 1.55, 1.69 1.00 0.96, 1.04 |
| 10 | 0 | 2.10 2.00, 2.21 1.15 1.10, 1.21 |
| 10 | 10 | 1.88 1.79, 1.97 0.92 0.87, 0.97 |
| 10 | 20 | 1.73 1.65, 1.81 0.94 0.90, 0.99 |
| 10 | 30 | 1.62 1.55, 1.69 0.96 0.91, 1.00 |
| 20 | 0 | 2.10 2.00, 2.21 1.29 1.23, 1.35 |
| 20 | 10 | 1.88 1.79, 1.97 1.07 1.02, 1.12 |
| 20 | 20 | 1.73 1.65, 1.81 0.88 0.84, 0.93 |
| 20 | 30 | 1.62 1.55, 1.69 0.92 0.87, 0.96 |
| 30 | 0 | 2.10 2.00, 2.21 1.42 1.35, 1.49 |
| 30 | 10 | 1.88 1.79, 1.97 1.20 1.15, 1.26 |
| 30 | 20 | 1.73 1.65, 1.81 1.03 0.98, 1.08 |
| 30 | 30 | 1.62 1.55, 1.69 0.87 0.83, 0.92 |

* Assuming that the true smoking-adjusted risk ratio between alcohol consumption and lung cancer is 1.0. 
† Risk ratio for alcohol consumption and lung cancer risk in relation to nondrinkers. 
‡ RR, risk ratio; CI, confidence interval. 
§ Adjusted for smoking by the Mantel-Haenszel method.

| TABLE 6. Results of second simulation of misclassification in cohort studies of alcohol consumption and lung cancer risk* |
|---------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Misclassification (%) | Simulated risk ratio† |  |
| From heavy smoker to light smoker | From heavy drinker to light drinker | Exposure category | Crude RR‡ 95% CI‡ | Smoking-adjusted RR§ 95% CI |
| 0 | 0 | Light drinkers | 1.73 1.63, 1.83 1.00 0.94, 1.06 |
| Heavy drinkers | 2.71 2.56, 2.86 1.00 0.94, 1.06 |
| 0 | 30 | Light drinkers | 1.89 1.79, 2.00 1.00 0.95, 1.06 |
| Heavy drinkers | 2.71 2.55, 2.88 1.00 0.94, 1.07 |
| 30 | 0 | Light drinkers | 1.73 1.63, 1.83 1.07 1.01, 1.14 |
| Heavy drinkers | 2.71 2.56, 2.86 1.10 1.04, 1.17 |
| 30 | 30 | Light drinkers | 1.89 1.79, 2.00 1.12 1.06, 1.18 |
| Heavy drinkers | 2.71 2.55, 2.88 1.02 0.95, 1.09 |

* Assuming that the true smoking-adjusted risk ratio between alcohol consumption and lung cancer is 1.0. 
† Risk ratio for alcohol consumption and lung cancer risk relative to nondrinkers. 
‡ RR, risk ratio; CI, confidence interval. 
§ Adjusted for smoking by the Mantel-Haenszel method.
TABLE 7. Summary of data from studies of alcohol consumption and lung cancer risk among nonsmokers

<table>
<thead>
<tr>
<th>Type of study, author(s), and year (ref.)</th>
<th>No. of subjects</th>
<th>Definition of a nonsmoker</th>
<th>Ethanol consumption (g/month)</th>
<th>Risk ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-control studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kabat and Wynder, 1984 (76)</td>
<td>134 cases</td>
<td>&lt;1 cigarette-year, pipe-year, or cigar-year (&lt;0.05 pack-years)</td>
<td>Nondrinker 250–999 ≥1,000</td>
<td>—*</td>
<td></td>
</tr>
<tr>
<td>134 controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mayne et al., 1994 (77)</td>
<td>413 cases</td>
<td>&lt;100 cigarettes during the past 10 years</td>
<td>Quartile 1 (reference) 1.00</td>
<td>1.06</td>
<td>0.87, 1.18</td>
</tr>
<tr>
<td>413 controls</td>
<td></td>
<td></td>
<td>Quartile 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koo, 1988 (78) (females)</td>
<td>88 cases</td>
<td>&lt;20 cigarettes or pipes in a lifetime</td>
<td>Nondrinker ≥52</td>
<td>1.0</td>
<td>0.93, 3.70</td>
</tr>
<tr>
<td>137 controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murata et al., 1996 (79) (males)</td>
<td>887 cases</td>
<td>No cigarettes during the previous 2 years</td>
<td>Nondrinker &lt;1,000</td>
<td>1.32</td>
<td>0.54, 3.24</td>
</tr>
<tr>
<td>1,774 controls</td>
<td></td>
<td></td>
<td>≥1,000</td>
<td>2.22</td>
<td>0.62, 6.08</td>
</tr>
<tr>
<td><strong>Cohort studies†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer Prevention Study I Males</td>
<td>84,674</td>
<td>Lifetime never smoker</td>
<td>Nondrinker 1.0</td>
<td>1.08</td>
<td>1.00, 1.18</td>
</tr>
<tr>
<td>Females</td>
<td>338,809</td>
<td></td>
<td>≥500</td>
<td>1.38</td>
<td>1.23, 1.53</td>
</tr>
<tr>
<td>Cancer Prevention Study II Males</td>
<td>58,943</td>
<td>&lt;1 cigarette-year, pipe-year, or cigar-year (&lt;0.05 pack-years)</td>
<td>Nondrinker 1.0</td>
<td>0.95</td>
<td>0.57, 1.59</td>
</tr>
<tr>
<td>Females</td>
<td>120,967</td>
<td></td>
<td>≥500</td>
<td>1.22</td>
<td>0.68, 2.20</td>
</tr>
</tbody>
</table>

* No significant difference.
† Previously unpublished results provided by the American Cancer Society.

(95 percent CI: 0.82, 6.08) was found among subjects consuming at least 1,000 g of ethanol per month relative to nondrinkers; however, former smokers who had quit smoking 2 or more years previously were considered nonsmokers. In the new analyses of nonsmokers in the CPS-I and CPS-II cohort studies, alcohol consumption categories were 1–499 and ≥500 g of ethanol per month, with nondrinkers used as the reference group. For CPS-I, a dose-response relation was observed, with RRs of 1.08 and 1.38, respectively, in men and 1.16 and 1.98, respectively, in women. However, for CPS-II, no association was seen; RRs were 0.95 and 1.22, respectively, in men and 1.30 and 0.57, respectively, in women. Therefore, overall, evidence from cohort and case-control studies of nonsmokers is mixed and provides no strong evidence for an association between alcohol drinking and lung cancer risk.

**Publication bias**

For cohort studies, case-control studies, and brewery worker studies, the adjusted rank correlation test (40) and regression asymmetry test (41) did not reveal any substantial evidence of publication bias (figures not shown). For the 15 studies of alcoholics, the two tests differed significantly. No evidence of publication bias was provided by visual examination of the adjusted rank correlation funnel plot or test statistic (p = 0.73) for the studies of alcoholics. In contrast, the regression asymmetry test suggested that publication bias may have occurred (p = 0.006).

**DISCUSSION**

Overall, the results of this study indicate that after adjustment for cigarette smoking, evidence of an association between alcohol consumption and lung cancer is largely limited to groups consuming ≥2,000 g of ethanol per month (more than five drinks per day). This level of consumption, in relation to nondrinkers, was associated with a pooled RR of 1.53 in cohort studies and a pooled odds ratio of 1.86 in case-control studies. Studies of brewery workers showed no substantial excess of lung cancer in relation to the general population, but the RR for lung cancer in studies of alcoholics was 1.99. Our sensitivity analyses demonstrated that the elevated RR in alcoholics could be explained by differences in the prevalence of smoking between alcoholics and the general population. For the cohort and case-control studies, we found in simulations that extremely high underascertainment of smoking exposure, without substantial misclassification of alcohol consumption, would be required to produce artificially elevated RRs of the magnitude observed in the highest consumption categories. However, among case-control studies, the evidence for an association between alcohol consumption and lung cancer risk was limited to the hospital-based studies. Population-based case-control studies did not show an association.

Our sensitivity analyses provided only limited evidence that residual confounding effects of smoking could completely explain the association observed in the highest alcohol consumption category. The conditions of our simulations...
were simple, and high levels of misclassification from “smoker” to “nonsmoker” may be unrealistic (80), especially in the presence of low drinking misclassification. Similarly, in the second part of our cohort study simulations, it may be unrealistic to postulate such disparate levels of misclassification for smoking and drinking. Nevertheless, our example demonstrates that if smoking misclassification is higher than drinking misclassification, the effect may be to inflate the smoking-adjusted RR, perhaps to levels comparable to the results observed in our meta-analysis.

Alcohol drinking is an established risk factor for carcinomas of the liver and upper aerodigestive tract. The postulated mechanisms are less likely to apply to lung cancer, however. Possible carcinogenic mechanisms for alcohol have been reviewed previously (2, 3, 5, 6, 8). The main intermediary metabolite of ethanol, acetaldehyde, has been shown to be a carcinogen in animals; in addition, human studies have shown an increased risk of alcohol-related cancers among subjects with genetic polymorphisms that lead to higher internal doses of acetaldehyde following alcohol exposure (81). Other possible mechanisms of carcinogenicity are more indirect: For example, alcoholic beverages may contain carcinogenic compounds. Alcohol may damage or increase the permeability of the oral cavity lining and other mucosa (82) and may enhance the activity of some carcinogens by increasing their solubility. In addition, alcohol consumption may suppress immune function (83), stimulate cell proliferation, or alter hormonal balance. Heavy drinking is associated with compromised liver function and therefore may result in reduced detoxification of carcinogens and reduced delivery of protective nutrients. Heavy drinking is also known to induce cirrhosis, which increases the risk of liver cancer (1). Finally, heavy drinkers are likely to substitute alcohol calories for calories obtained from food and may therefore consume fewer protective foods such as fruits and vegetables.

Results within study design were largely homogeneous. We noted, however, that results from three studies based on intervention trials (one nested case-control study (70) and two cohort studies (63, 66)) differed markedly from those of most other studies. None of these three studies showed a positive association between alcohol consumption and lung cancer, even in analyses unadjusted for smoking. In one of these studies, in which subjects were matched according to smoking status (70), a substantial inverse association was observed between alcohol and lung cancer. It is possible that these heterogeneous results can be attributed to the effects of the intervention trials or to decisions regarding selection into the trials. Two of these studies provided results adjusted for smoking (66, 70); when we excluded these studies from our smoking-adjusted pooled analyses, the results were similar (data not shown).

Standard tests did not reveal any evidence of publication bias in the cohort or case-control studies. Despite this, we are aware of at least two forms of publication bias in our meta-analysis, both of which may have artificially inflated the pooled RRs. First, we are aware of published cohort studies on alcohol consumption which do not mention lung cancer (e.g., CPS-I (15) and CPS-II (16)) and published case-control studies on lung cancer which do not mention alcohol consumption. In some of these studies, an analysis of alcohol and lung cancer may have been performed but not published because of null findings. In the second form of publication bias, we are aware of several sets of results that provided evidence against a relation between alcohol and lung cancer but could not be included in our meta-analysis because of insufficient data being presented in the publication. In two cohort studies (84, 85) and three case-control studies (13, 86, 87), unadjusted results showed an association between alcohol and lung cancer which vanished after controlling for smoking. In one case-control study (88), no association was observed before or after controlling for smoking; and the authors of one study of 935 alcoholics (89) simply reported that the observation of nine lung cancer deaths was not significantly different from the expected number. We were able to include unadjusted results from one of these studies (13) in our meta-analysis. The further inclusion of the other results would have decreased the pooled smoking-adjusted RRs observed in our meta-analysis, increasing the plausibility of residual confounding as an explanation for the observed excesses of lung cancer.

Residual confounding by active cigarette smoking may be most likely in the highest alcohol consumption category, because of an excess of extremely heavy smokers among the cases. An example of this phenomenon can be found in table 4 in one of the publications identified for this meta-analysis (71). This type of residual confounding was not explicitly addressed in our simulations of misclassification. However, in our meta-analysis of cohort study results, only the highest alcohol consumption category showed a notable excess of lung cancer in relation to nondrinkers, increasing the plausibility that residual confounding can explain the observed excesses of lung cancer in heavy drinkers.

In conclusion, results from these studies of nonsmokers, brewery workers, and alcoholics do not support an association between alcohol consumption and lung cancer. Results from population-based case-control studies did not show any association, although a dose-response relation was observed in hospital-based case-control studies. For cohort studies, we observed a smoking-adjusted excess of lung cancer (RR = 1.53) in our highest alcohol consumption category (approximately five or more drinks per day) relative to nondrinkers. These results should be interpreted cautiously, because the highest consumption category in any study may be the most vulnerable to residual confounding within that category. In addition, very few studies presented data on persons who consumed more than five drinks per day, which limited our ability to draw clear conclusions about risk. The results of our sensitivity analyses indicated that if underascertainment of smoking is much more likely than underascertainment of drinking, the observed smoking-adjusted RR will be inflated above 1.0 even if the true RR is 1.0. If levels of smoking misclassification and drinking misclassification are comparable, however, this effect appears insufficient to explain our observed excess of lung cancer in the highest alcohol consumption category. Thus, we are unable to exclude the possibility of a relation between very high levels of alcohol consumption and an increased risk of
lung cancer. However, at consumption levels below five drinks per day, the weight of the evidence suggests that alcohol drinking does not increase the risk of lung cancer and that confounding by cigarette smoking is responsible for the observed associations.

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REFERENCES