Associations between Beer, Wine, and Liquor Consumption and Lung Cancer Risk: A Meta-analysis

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Abstract

Objective: **Epidemiologic studies suggest that the effect on lung cancer risk may be different for beer, wine, and liquor. We conducted dose-specific meta-analyses and dose-response meta-regression to summarize findings from the current literature on the association between consumption of beer, wine, or liquor and lung cancer risk.**
Results: **Average beer consumption of one drink or greater per day was associated with an increased risk of lung cancer [relative risk (RR), 1.23; 95% confidence interval (95% CI), 1.06-1.41]. This association was observed in both men and women, although it was only significant in men. A J-shaped dose-response curve was suggested for beer intake. An inverse association was observed for both average wine consumption of less than one drink per day (RR, 0.77; 95% CI, 0.59-1.00) and one drink or greater per day (RR, 0.78; 95% CI, 0.60-1.02) in the drinking range incurred in the source studies. Average liquor consumption of one drink or greater per day was found to be associated with increased risk in men (RR, 1.33; 95% CI, 1.10-1.62). No association was observed for liquor drinking in women. The presence of heterogeneity between studies was detected. Study design, country, gender, adjustment factors, and lung cancer histologic type were not significant predictors of the heterogeneity.**
Conclusions: **The results from this meta-analysis suggest that high consumption of beer and liquors may be associated with increased lung cancer risk, whereas modest wine consumption may be inversely associated with risk. More research with improved control of confounding is needed to confirm these findings and to establish the dose-response relationship, particularly risk at high consumption levels.** (Cancer Epidemiol Biomarkers Prev 2007;16(11):2436–47)

Introduction

Lung cancer is the most common newly diagnosed cancer and cause of cancer deaths in the world. Although tobacco smoking is the most important etiologic factor for the disease, a significant portion of lung cancer cases cannot be attributed to tobacco smoking alone (1). Alcoholic beverage consumption has been established as a human carcinogen for several cancers, including cancers of the mouth, pharynx, larynx, esophagus, liver, colon, rectum, and female breast (2). A possible link between alcohol consumption and risk of lung cancer has long been speculated (3). However, despite the effort of large prospective studies, meta-analyses, and pooled analyses (4-8), epidemiologic studies have not provided consistent evidence on the effect of alcohol drinking on lung cancer.

Although disentangling the effects of alcohol and tobacco has been a challenging task and various degree of residual confounding could potentially explain the discrepancies, the conflicting findings may also be due to true heterogeneity among studies. Several studies examining the consumption of different types of alcoholic beverages suggest that the effect on lung cancer risk might be different for beer, wine, and liquors (9-11). Although ethanol is the common ingredient in all alcoholic beverages, the presence and concentrations of carcinogenic compounds, including nitrosamines (arising from the brewing process), polycyclic aromatic hydrocarbons (PAH), asbestos filtration products, and arsenic pesticide residues, differ among beer, wine, and liquors (12-14). For example, nitrosamines have been found at a higher concentration in beer than in whiskies (15). On the other hand, the presence and activity of compounds that work against carcinogenesis, like antioxidative vitamins, polyphenols, and selenium, also vary among types of beer, wine, and liquors (16-18).

These data suggest that the inconsistent associations previously observed could be partly due to the different compositions of alcoholic beverages consumed by the study populations. However, a comprehensive quantitative review on the separate effects of beer, wine, and liquor has not been previously done. In this study, we conducted meta-analyses to summarize findings from the current epidemiologic literature on beer, wine, and liquor intake and lung cancer risk and to identify gaps in the literature to help direct future research.

Materials and Methods

Identification of Studies. We first conducted a comprehensive search to identify epidemiologic studies examining the associations between any kind of alcohol

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use (total or specific types) and lung cancer risk. Studies published before February 2007 were identified by searching the PubMed database using the following keywords in the title/abstract text: ''alcohol (title),'' ''ethanol (title),'' ''alcoholic (title),'' ''alcoholics (title),'' ''beer,'' ''wine,'' ''liquor,'' in combination with ''lung cancer,'' ''lung carcinoma,'' ''lung incidence,'' and ''lung mortality.'' We then reviewed the references cited by each article identified from the database search for additional studies. Studies that examined the consumption of at least one type of alcoholic beverage (beer, wine, or liquor) and lung cancer risk were included for this analysis. We excluded studies that did not have individual level data. Studies that did not provide smoking-adjusted estimates or the appropriate measure of precision [95% confidence intervals (95% CI) or SE] were also excluded. When there was overlapping in the study populations of the published papers, the latest study was included unless indicated otherwise.

Data Extraction and Conversion. For each study, the following information was extracted when possible and applicable: publication date, type of study (cohort or case-control), country where the study was conducted, study period, age, gender and ethnicity of the subjects, method of epidemiologic data collection, description of the cohort, source of cases and controls, matching, response rate, follow-up rate, proportion of cases histologically confirmed, distribution of lung cancer histologic type among cases, adjusted risk estimates, 95% CIs, and adjustment factors. Odds ratios from case-control studies and rate ratios from cohort studies were used as lung cancer risk ratio estimates because lung cancer is a rare disease. We would also like to note that the case-control studies used recent consumption patterns collected at a time before diagnosis to assess alcohol exposure, whereas the cohort studies used consumption information at baseline.

Most studies used the amount consumed over a time period (e.g., number of drinks per week or milliliters of ethanol per month) as the exposure measurement. To standardize the unit of consumption for dose-specific analysis, the following formularies were used for the conversion: standard size for one serving of 330 mL of beer per bottle, 150 mL of wine per glass, and 40 mL of liquor per shot. Each standard serving contains ~13 g of ethanol, or equivalently, 18 mL of ethanol. Whiskey, vodka, and spirits were grouped as liquors.

Data Analysis. We first examined whether consumption of each type of alcoholic beverage could potentially increase the risk of lung cancer. To do this, we extracted and combined the risk estimates for the highest drinking category from each study. We then examined the dose-specific summary risk estimates for two drinking categories using one drink per day (13 g of ethanol) as the cutoff. Summary relative risks (RRs) were calculated for average consumption of less than one drink per day and for average consumption of one drink or greater per day compared with nondrinkers. This cutoff was chosen based on the exposure categories used in the studies identified so that we could include most estimates in the analysis and on the knowledge that alcohol drinking possesses a J-shaped relationship with coronary heart disease risk, with one to two drinks per day being the turning point (19). Using this cutoff, a single study may have multiple estimates that fall in a category. In this case, an inverse variance–weighted average of these multiple estimates was used in the meta-analysis. Estimates from drinking categories that spanned across the one-drink-per-day cutoff (e.g., 1-14 drinks per week or open-ended categories such as ≥2 drinks per week) were excluded from this analysis. Studies that reported only qualitative frequencies of use (5, 20) or drinking status (21) were also excluded from this dose-specific analysis.

Summary risk estimates were calculated for all studies combined, as well as by subgroup. We did analyses stratified by study design (case-control and cohort), gender (when gender-specific estimates were available), geographic region, whether the study indicated the adjustment for the other two types of alcoholic beverages, and quality of smoking adjustment. Studies that had better adjustment for smoking were those that adjusted for current smoking status and/or duration since quitting in addition to pack-year smoked. When heterogeneity was detected in dose-specific analyses after stratification by gender, two methods were used to investigate the source of heterogeneity. First, meta-regression was used to explore factors affecting the RR estimates. We examined study design, year of publication, geographic region, adjustment for pack-year of smoking, better adjustment for smoking, adjustment for the other two types of alcoholic beverages, and proportion of adenocarcinoma among cases as potential explanatory variables. Second, we used a graphical method proposed by Galbraith (22), in which the z statistic is plotted against the reciprocal SE, to examine the contribution of heterogeneity by each study. For influence analysis, the potential outlier studies were excluded one at a time to determine their magnitude of influence on the overall summary estimate. We considered the outlier study influential if the exclusion of it changed our conclusion or the effect estimate by at least 20%.

To explore the dose-response relationship between lung cancer and alcohol consumption, especially for higher levels of consumption, we used the ''pre-pool'' method for trend estimation described by Greenland and Longnecker (23). In these analyses, the natural logarithm of the adjusted RR for each non-reference drinking category from each study were pooled and regressed as a function of the drinking level using weighted least squares regression models and corrected for covariance between estimates from the same study. One study (24) was excluded from this analysis because it did not provide the number of subjects or person time for each drinking category to perform the correction (23). Studies that reported only qualitative frequencies of use (5, 20) or drinking status (21) were also excluded from this analysis. We used the midpoint of the drinking category for the regression. For open-ended categories, we used the mean consumption for this category where available, or we assumed that the open-ended categories were of the same amplitude as the preceding category and assigned the midpoint accordingly. For fitting the dose-response curve, we fitted a family of second-degree fractional polynomial models (25). All models were fitted using random effects models. The best-fitting model was chosen based on the deviance test against the linear model. Overall model fit was assessed using the goodness-of-fit test.

Table 1. Summary of case-control studies of types of alcoholic beverages and lung cancer risk

First author (year of publication)	Country	Control source	Gender	Cases/ histologic type*	Controls
Mettlin (1989)	United States	Hospital controls	Men and women	569 NR	569
Bandera (1992)	United States	Neighborhood controls	Men	280 NR	564
De Stefani (1993)	Uruguay	Hospital controls	Men	327 SCC: 46% AD: 25% SCLC: 18%	350
Carpenter (1998)	United States	Population controls	Men and women	261 SCC: 23% AD: 33% SCLC: 12%	615
De Stefani (2002)	Uruguay	Hospital controls	Men	160 AD: 100%	520
Hu (2002)	Canada	Population controls	Women	161 SCC: 6% AD: 54% SCLC: 6%	483
Freudenheim (2003)	United States	Population controls	Men and women	273 NR	3,351
Ruano-Ravina (2004)	Spain	Hospital controls	Men and women	132 SCC: 55% AD: 20% SCLC: 15%	187
Kubik (2004)	Czech Republic	Relatives or friends of other patients	Women	435 SCC: 26% AD: 35% SCLC: 23%	1,710
Benedetti (2006)	Canada	Population controls	Study I		
			Men	699 SCC: 41% AD: 20% SCLC: 19%	507
			Study II		
			Men	640 SCC: 33% AD: 35% SCLC: 16%	861
			Women	454 SCC: 19% AD: 48% SCLC: 16%	607

*Lung cancer histologic type. SCC, squamous cell carcinoma; AD, adenocarcinoma; SCLC, small cell lung cancer; NR, not reported.
†Reference group for comparison: nondrinkers, unless otherwise indicated.
‡Reference group may include occasional drinkers.

Statistical Methods. Summary estimates for the adjusted odds ratios or rate/risk ratios were calculated with the statistical program STATA (version 9; ref. 26). For each analysis, data were combined using inverse-variance weighting with the random effects model. Heterogeneity between studies was examined using the Mantel-Haenszel test for heterogeneity. A P value of <0.05 was used as an indication of the presence of heterogeneity. The pre-pool weighted least-squares meta-regression with correction for within-study correlation was done in STATA (version 9) using the glst command (27). The validity of the meta-analysis results greatly depends on the absence of publication bias. Publication bias, therefore, was assessed by the regression asymmetry test of Egger et al. (ref. 28; $P < 0.05$ as an indication for publication bias) and by visual inspection of the Begg's funnel plot.

Results

We identified a total of 17 published case-control studies that reported the association between the consumption of beer, wine, and/or liquor and risk of lung cancer (20, 21,

Table 1. Summary of case-control studies of types of alcoholic beverages and lung cancer risk (Cont'd)

Highest consumption category/relative risk [†] (95% CI)			Adjustment factors	Reference
Beer	Wine	Liquor		
≥10 drinks/wk 1.3 (0.8-2.1)	≥10 drinks/wk 1.0 (0.4-2.5)	≥10 drinks/wk 0.7 (0.4-1.1)	Age, sex, education, residence, smoking (likely pack-year) and β-carotene intake	39
≥12 drinks/mo 1.6 (1.0-2.4)	≥2 drinks/mo 0.7 (0.5-1.1)	≥9 drinks/mo 1.1 (0.7-1.6)	Age, education, and smoking (pack-years)	29
(ethanol) ≥60 mL/d 3.4 (1.3-15.2)	(ethanol) ≥121 mL/d 1.5 (0.9-3.3)	(ethanol) ≥116 mL/d 1.1 (0.6-1.4)	Age, education, residence, smoking (pack-years), and other types of alcoholic beverages	32
≥1 drink/d 0.9 (0.4-1.8) [†]	≥1 drink/d 0.8 (0.3-1.9) [‡]	≥1 drink/d 1.9 (1.0-3.4) [‡]	Age, sex, race, smoking (pack-years and years since quitting), other types of alcoholic beverages, and saturated fat consumption	31
(ethanol) ≥61 mL/d 0.6 (0.3-1.6)	(ethanol) ≥121 mL/d 0.4 (0.2-1.1)	(ethanol) ≥121 mL/d 1.4 (0.7-3.0)	Age, education, residence, smoking (smoking status, cigarettes per day, years since quitting and age at starting), total alcohol intake, body mass index (BMI) and family history of lung cancer.	33
>0.5 drink/wk 0.5 (0.2-1.1)	>0.5 drink/wk 0.7 (0.4-1.2)	>0.5 drink/wk 1.1 (0.6-2.1)	Age, education, residence, and social class. Never-smokers only	35
(in previous 12-24 mo, ethanol) >1.6 L 1.7 (0.4-1.4)	(in previous 12-24 mo, ethanol) >1.0 L 0.7 (0.4-1.3)	(in previous 12-24 mo, ethanol) >1.0 L 0.9 (0.5-1.5)	Age, sex, race, education, smoking (packs per year and years smoked), passive smoking, BMI, and dietary intake	34
Drinkers 1.1 (0.6-2.1)	Drinkers 0.5 (0.2-1.4)	Drinkers 1.6 (0.8-3.4)	Age, sex, occupation, smoking (lifetime tobacco consumption) and total alcohol intake	21
>once a week 1.0 (0.7-1.5)	>once a month 0.6 (0.4-0.9)	Drinkers 0.7 (0.5-1.0)	Age, education, residence and smoking (pack-years)	20
≥7 drinks/wk 1.5 (1.1-2.1) [‡]	≥7 drinks/wk 0.7 (0.4-1.1) [‡]	≥7 drinks/wk 1.2 (0.8-1.7) [‡]	Age, race, education, census tract income, smoking (smoking status, cigarette-years and time since quitting) and respondent status	30
1.0 (0.7-1.4) [‡]	0.8 (0.5-1.1) [‡]	0.9 (0.7-1.3) [‡]		
0.9 (0.5-1.6) [‡]	0.7 (0.4-1.2) [‡]	1.7 (0.8-3.5) [‡]		

29-43). William et al. (42) and Mayne et al. (38) did not provide 95% CIs and were excluded from the analysis. Rachtan and Sokolowski (40) and Rachtan (41) did not provide smoking-adjusted estimates and were excluded. Finally, ref. (37) seemed to be an updated analysis of refs. (20, 36, 43). However, ref. (20) reported odds ratios (OR) by frequency of drinking, whereas ref. (37) only reported OR by drinking status. Therefore, ref. (20) was included in the meta-analysis, and refs. (36, 37, 43) were excluded. Characteristics of the 10 included case-control studies are summarized in Table 1. Benedetti et al. (30) reported results from two independent case-control studies (referred to as study I and study II). Six of the 10 studies were conducted in the United States or Canada, and two were conducted in Europe and South America (Uruguay) each. The 10 case-control studies included a combined total of 4,391 cases and 10,324 controls.

We identified a total of six published cohort studies that reported the association between consumption of beer, wine, and/or liquor and risk of lung cancer (5, 7, 9, 10, 24, 44). Freudenheim et al. (9) is a pooled analysis of data from seven cohort studies, which included the cohorts used in Potter et al. (7) and Woodson et al. (44). Potter et al. (7) and Woodson et al. (44) were therefore excluded from the analysis. The characteristics of the four included cohort studies are summarized in Table 2. All studies were conducted in the United States or Europe. These studies included a combined total of 453,751 participants, from which 4,119 lung cancer cases arose.

Table 2. Summary of cohort studies of types of alcoholic beverages and lung cancer risk

First author (year of publication)	Country	Cohort description	Cases/histologic type*
Pollack (1984)	United States	Japan-Hawaii Cancer Study: 8,006 Japanese men who were born between 1900 and 1919	89 NR
Chow (1992)	United States	Cohort of 17,818 White men 35 y or older who were life-insurance policy-holders of the Lutheran Brotherhood Insurance Society	219 NR
Prescott (1999)	Denmark	The Copenhagen City Heart Study, the Centre of Preventive Medicine, and the Copenhagen Male Study: 28,160 (15,107 men and 13,053 women) subjects were included in this study	Men 480 NR Women 194 NR
Freudenheim (2005)	United States, Canada, Europe	Pooled analysis based on seven cohort studies: α-Tocopherol β-Carotene Cancer Prevention Study (men); Canadian National Breast Screening Study (women); Health Professional Study (men); Iowa Women's Health Study (women); Netherlands Cohort Study (both sexes); New York State Cohort (both sexes); Nurses' Health Study (women). Total of 399,767 participants (137,335 men and 262,432women).	Men 1,762 SCC: 37% AD: 21% SCLC: 16% Women 1,375 SCC: 18% AD: 42% SCLC: 19%

*Lung cancer histologic type. SCC: squamous cell carcinoma; AD: adenocarcinoma; SCLC: small cell lung cancer; NR: not reported.
†Reference group for comparison: nondrinkers, unless otherwise indicated.
‡Compared with <1 drink/wk.

Beer. Results from the meta-analyses for all studies combined and by subgroup are presented in Table 3. The meta-analysis for all studies showed a positive association between beer drinking and lung cancer risk when the estimates of the highest beer-drinking category from each study were combined (RR, 1.23; 95% CI, 1.06-1.41). When we examined the dose-specific summary estimates, the increased risk was only observed with average beer drinking of one drink or greater per day (RR, 1.25; 95% CI, 1.06-1.48). For average beer drinking of less than one drink per day, an inverse association was suggested (RR, 0.78; 95% CI, 0.64-0.95). This J-like pattern for the dose-specific risk estimates was found in both case-control and cohort studies. In the gender-specific analysis, the positive association for average beer drinking of one drink or greater per day was only significant among men (RR, 1.20; 95% CI, 0.99-1.46). An increased risk was suggested among women, although the confidence interval was wide (RR, 1.43; 95% CI, 0.89-2.30). Similar risk estimates were also observed when analyses were restricted to U.S./Canadian studies and to studies that adjusted for the other two types of alcoholic beverages. When we restricted to studies that had better adjustment for smoking, the effect estimates were not significant and slightly attenuated for the highest drinking category (Table 3).

The presence of heterogeneity was detected among study results in women. Of the previously mentioned factors explored in the meta-regression, none was found to significantly explain the heterogeneity. Based on the Galbraith plot, Benedetti et al. (30) seemed to contribute most to the heterogeneity of the results. Removing this outlier study increased the RR estimate to 0.93 [0.81-1.08] for women consuming less than one drink per day.

In the dose-response analysis, the best fitted model suggested a J-shaped dose-response curve for beer intake and lung cancer risk, although the 95% CIs included unity (Fig. 1). The goodness-of-fit test, however, detected poor fit of the model to the data (Q = 58.12, P value <0.01).

Wine. An inverse association for wine drinking and lung cancer risk was observed when all studies were combined and in all subgroup analyses (Table 3). The inverse association was suggested for both the average drinking level of less than one drink per day (for all studies: RR, 0.77; 95% CI, 0.59-1.00) and for one drink or greater per day (for all studies: RR, 0.78 95% CI, 0.60-1.02). In the gender-specific analyses, an inverse association was marginally significant among women only when the highest drinking categories were combined (RR, 0.75; 95% CI, 0.54-1.04). In men, the inverse association was observed for average wine drinking of one glass or greater per day (RR, 0.76; 95% CI, 0.56-1.03).

Heterogeneity among study results was detected in both men and women. Study characteristics, however, did not explain the heterogeneity in the meta-regression models. The Galbraith plot showed that Benedetti et al. (30) was the outlier study (for less than one drink per day) among women. In men, Benedetti et al. (studies I and II; ref. 30) appeared as the outlier studies for less than one drink per day, and De Stefani (32) was an outlier for one drink or greater per day. Among women, exclusion of Beneditti et al. (30) increased the RR to 0.83

Table 2. Summary of cohort studies of types of alcoholic beverages and lung cancer risk (Cont'd)

Highest consumption category/relative risk [†] (95% CI)			Adjustment factors	Reference
Beer	Wine	Liquor		
≥500 oz/mo 1.1 (0.7-2.1)	≥50 oz/mo 2.2 (1.0-4.4)	≥50 oz/mo 2.6 (1.3-5.0)	Age, smoking (current status) and other types of alcoholic beverages (if significant)	24
>13 times/mo 1.1 (0.6-1.9)		>13 times/mo 1.0 (0.5-1.8)	Age, occupation, and smoking (smoking status, past daily cigarette use, and current daily cigarette use)	5
>13 drinks/wk 1.4 (1.0-1.8) [‡] 1.5 (0.7-3.1) [‡]	>13 drinks/wk 0.4 (0.2-0.9) [‡] 0.2 (0.0-1.3) [‡]	>13 drinks/wk 1.5 (1.0-2.1) [‡] 0.7 (0.2-2.2) [‡]	Age, education, study cohort, smoking (current smoking: pack-year and duration), total alcohol consumption and other types of alcoholic beverages	10
(ethanol) ≥15 g/d 1.1 (0.9-1.4) 1.9 (1.5-2.4)	(ethanol) ≥15 g/d 0.9 (0.6-1.4) 1.1 (0.8-1.5)	(ethanol) ≥15 g/d 1.3 (1.1-1.7) 1.0 (0.8-1.2)	Education, smoking (smoking status, duration, and daily cigarettes smoked), other types of alcoholic beverages, BMI, and energy intake	9

(95% CI, 0.71-0.97) for those drinking less than one drink per day. Among men, exclusion of the outlier studies did not change the effect estimates by at least 20%.

In the dose-response analysis, the model-predicted relative risk was generally under unity in the range of wine drinking incurred in the original studies (Fig. 2). The goodness-of-fit test, however, detected poor model fit (Q = 65.54, P value <0.01).

Liquor. Average liquor consumption of one drink or greater per day was found to be significantly associated with increased lung cancer risk for all studies combined (RR, 1.25; 95% CI, 1.04-1.51) and for the cohort studies (RR, 1.41; 95% CI, 0.99-1.99; Table 3). In case-control studies, a positive association was suggested, although the confidence interval included one (RR, 1.19; 95% CI, 0.91-1.56). A positive association for consuming at least one liquor drink per day was observed among men (RR, 1.33; 95% CI, 1.10-1.62). No association between liquor drinking and lung cancer risk was found among women.

Heterogeneity among study results was suggested for both levels of liquor drinking in men and for consumption of less than one drink per day in women. No significant contributor to the heterogeneity was identified from the meta-regression. The Galbraith plot suggested that Benedetti et al. (30) contributed most to the heterogeneity of results for liquor drinking among women. In men, Bandera et al. (29) was the main source for heterogeneity for less than one drink per day, whereas Benedetti et al. (study II; ref. 30) and Pollack et al. (24) both seemed to be outlier studies for one drink or greater per day. Among women, exclusion of the Benedetti et al. (30) study increased the summary estimate to 0.85 (0.74-0.98) for those drinking less than one drink per day. Among men, removal of outlier studies did not change the effect estimates by at least 20%.

Because results from the dose-specific analysis suggested possible effect modification by gender for liquor consumption, we fitted separate dose-response curves for men and women. In men, the dose-response curve based on the best fitted model was a downward U shape (Fig. 3A). The goodness-of-fit test, however, detected poor fit of the model to the data (Q = 30.59, P value = 0.01). In women, liquor drinking seems to be protective at low levels but quickly increases risk beyond three drinks per day (Fig. 3B). However, the data for this analysis were sparse, such that the dose-response curve for women was fitted using only four studies and nine dose-response observations.

From examination of the Begg's funnel plots and Egger's tests, we were unable to detect any sign of publication bias for all three types of alcoholic beverages. The Egger's test P value for beer, wine, and liquor were 0.19, 0.76, and 0.83, respectively.

Discussion

We found that consumption of different types of alcoholic beverages at different levels was associated with different lung cancer risk. Using an average of one drink per day as the cutoff, the results of our meta-analyses suggest that average beer and liquor drinking of this level or higher may be associated with a 20% to 30% increase in risk among men. Average consumption of any type of alcoholic beverage of less than one drink per day does not seem to be adversely associated with lung cancer risk. For wine consumption, an inverse association was consistently observed. Comparing gender-specific results, we did not find any apparent discrepancies in the associations for beer or wine drinking among men and women. However, for daily liquor consumption of one drink or greater, a positive association was found in men but not in women. The reason for this difference is unclear, although it may be due to greater consumption among men than women in this open-ended category. On the other hand, the downward U-shaped dose-response curve observed for liquor consumption also renders the liquor association in men less clear.

Our results should be interpreted carefully in light of the limitation of potential residual confounding. Associations between preference of alcoholic beverage types and cigarette consumption have been consistently reported. In the United States, wine drinking has been associated with lower cigarette consumption. In the UNC Alumni Heart Study, the prevalence of cigarette smoking was 6.1%, 9.6%, 22.0%, and 9.8% among male drinkers who preferred wine, beer, liquors, and nondrinkers, respectively (45). Similar figures were observed for women. Although all studies included in this analysis adjusted for tobacco smoking, most studies only adjusted

Table 3. Summary estimates for alcoholic beverage types and lung cancer risk by subgroup

	Average consumption	Beer		
		Number of papers (studies)*	RR (95% CI)†	P‡
All studies	<1 drink/d	9 (16)	0.78 (0.64-0.95)	0.01
	≥ 1 drink/d	8 (15)	1.25 (1.06-1.48)	0.11
	Highest category§	14 (21)	1.23 (1.06-1.41)	0.08
Case-control	<1 drink/d	7 (8)	0.77 (0.59-1.02)	0.01
	≥ 1 drink/d	5 (6)	1.15 (0.85-1.55)	0.08
	Highest category	10 (11)	1.16 (0.94-1.43)	0.06
Cohort	<1 drink/d	2 (8)	0.84 (0.64-1.10)	0.24
	≥ 1 drink/d	3 (9)	1.39 (1.21-1.61)	0.66
	Highest category	4 (10)	1.37 (1.19-1.58)	0.69
Men	<1 drink/d	5 (12)	0.92 (0.81-1.04)	0.36
	≥ 1 drink/d	6 (13)	1.20 (0.99-1.46)	0.15
	Highest category	8 (15)	1.23 (1.04-1.45)	0.19
Women	<1 drink/d	3 (9)	0.68 (0.31-1.50)	<0.01
	≥ 1 drink/d	3 (9)	1.43 (0.89-2.30)	0.07
	Highest category	5 (11)	1.12 (0.73-1.74)	<0.01
United States/Canada	<1 drink/d	7 (8)	0.76 (0.58-1.00)	<0.01
	≥ 1 drink/d	4 (5)	1.16 (0.95-1.42)	0.32
	Highest category	8 (9)	1.20 (0.98-1.45)	0.15
Clearly adjusted for other two types of alcoholic beverages	<1 drink/d	4 (10)	0.64 (0.40-1.02)	0.03
	≥ 1 drink/d	5 (11)	1.37 (1.15-1.63)	0.32
	Highest category	5 (11)	1.37 (1.15-1.63)	0.32
Better adjustment for tobacco smoking‖	<1 drink/d	3 (10)	0.85 (0.67-1.08)	<0.01
	≥ 1 drink/d	3 (10)	1.20 (0.90-1.58)	<0.01
	Highest category	4 (11)	1.10 (0.83-1.49)	<0.01

*Number of papers (number of studies): There were seven cohort studies in the pooled analysis by Freudenheim et al. (9); the pooled estimates were used in the meta-analyses because estimates from individual studies were not reported in the paper. There were two independent case-control studies reported separately in Benedetti et al. (30).
†All pooled RRs are calculated from random-effects model. Reference group: nondrinkers (reference group in studies refs. 10, 30, 31 may include occasional drinkers).
‡P value for test of heterogeneity.
§Included studies that reported risk estimates by drinking status only.
‖Better adjustment for tobacco smoking includes studies that included never-smokers only or that adjusted for current smoking status and/or duration since quitting for former smokers, in addition to pack-years smoked.

for pack-year of smoking. It is well known that adjusting for pack-year only serves as an imperfect control for the effects of tobacco smoking. The inability to exclude residual confounding by tobacco smoking for the associations observed in our study, particularly the inverse association for wine, is an important limitation. Given the difficulty to completely remove confounding by tobacco smoking in observational epidemiologic studies of alcohol use and lung cancer, studies on populations homogeneous in smoking exposure (e.g., never smokers or heavy smokers) or simulation/sensitivity analyses (46) may provide further insight on this subject.

In addition to tobacco smoking, other sources of residual confounding also deserve attention. There are few studies that adjusted for dietary factors and environmental exposures (such as second-hand smoke and occupational exposures). Although somewhat controversial, dietary factors such as red meat consumption, fat intake, and intake of fruits and vegetables have also been linked to lung cancer risk (47-51). Furthermore, consumption of a specific type of alcohol may be related to certain dietary patterns. For example, beer and liquor drinkers may tend to consume more meat and fried foods, and less fruits and vegetables (52, 53). Also, wine drinking in the US is associated with higher socioeconomic status, higher consumption of fruits and vegetables, and lower fat intake (45, 53, 54). These observations suggest that alcoholic beverage consumption may be part of a health related lifestyle pattern that may affect lung cancer risk, including socioeconomic status and occupations. This signifies the importance of accounting for these associations. We only identified one study (Freudenheim et al. ref. 34) that adjusted for total energy intake and consumption of fruits and vegetables, in addition to passive smoking exposure. Based on the subjects' total consumption in the prior one to 2 years, the study found a positive association for beer drinking of >1.6 liter of ethanol (~90 drinks), an inverse association for wine drinking of greater than one liter of ethanol (~55 drinks), and no association for liquor drinking (Table 1).

Another limitation of our analysis is that we were unable to examine the relative risk for former drinkers, due to the lack of such estimates in the source materials. In most of our source studies, former drinkers were included in the nondrinker category (which was the reference group for their analyses). To our knowledge, the effect of former drinking by alcoholic beverage type on lung cancer risk has not been previously reported. There are epidemiologic and laboratory evidence suggesting that ethanol may act as a tumor promoter, rather than initiator (7, 11, 55). Therefore, recent drinking pattern seems to be a relevant exposure to examine. In a study where the associations for current and former drinking were both examined, no association was found for former alcohol consumption (OR = 0.90 [0.65-1.26]),

Table 3. Summary estimates for alcoholic beverage types and lung cancer risk by subgroup (Cont'd)

Wine			Liquor		
Number of papers (studies)*	RR (95% CI) †	P ‡	Number of papers (studies)*	RR (95% CI) †	P ‡
8 (15)	0.77 (0.59-1.00)	<0.01	8 (17)	0.89 (0.74-1.08)	<0.01
7 (14)	0.78 (0.60-1.02)	0.03	8 (15)	1.25 (1.04-1.51)	0.02
13 (20)	0.79 (0.65-0.95)	0.05	14 (21)	1.08 (0.95-1.23)	0.07
6 (7)	0.73 (0.50-1.05)	<0.01	6 (7)	0.86 (0.65-1.13)	<0.01
5 (6)	0.80 (0.60-1.07)	0.14	5 (6)	1.19 (0.91-1.56)	0.03
10 (11)	0.73 (0.63-0.86)	0.76	10 (11)	1.03 (0.87-1.23)	0.15
2 (8)	0.86 (0.77-0.95)	0.45	2 (8)	0.97 (0.88-1.07)	0.71
2 (8)	0.66 (0.27-1.65)	0.01	3 (9)	1.41 (0.99-1.99)	0.06
3 (9)	0.95 (0.44-2.04)	<0.01	4 (10)	1.18 (1.03-1.34)	0.66
4 (11)	0.94 (0.72-1.21)	0.01	4 (11)	1.01 (0.82-1.24)	0.04
5 (12)	0.76 (0.56-1.03)	0.05	6 (13)	1.33 (1.08-1.63)	0.04
7 (14)	0.84 (0.63-1.12)	0.04	8 (15)	1.20 (1.06-1.36)	0.55
3 (9)	0.56 (0.28-1.14)	<0.01	3 (9)	0.70 (0.40-1.22)	<0.01
3 (9)	0.79 (0.45-1.41)	0.09	3 (9)	1.05 (0.76-1.45)	0.30
5 (11)	0.75 (0.54-1.04)	0.10	5 (11)	0.94 (0.73-1.22)	0.20
7 (8)	0.76 (0.53-1.07)	<0.01	7 (8)	0.88 (0.69-1.13)	<0.01
3 (4)	0.76 (0.59-0.98)	0.96	4 (5)	1.24 (0.84-1.81)	0.01
7 (8)	0.80 (0.65-0.98)	0.30	8 (9)	1.05 (0.89-1.25)	0.36
3 (9)	0.85 (0.77-0.94)	0.64	3 (9)	0.98 (0.89-1.07)	0.72
4 (10)	0.86 (0.54-1.38)	0.02	5 (11)	1.35 (1.08-1.69)	0.10
5 (11)	1.00 (0.61-1.64)	0.01	5 (11)	1.20 (1.06-1.36)	0.46
3 (10)	0.72 (0.52-0.99)	<0.01	3 (10)	0.89 (0.69-1.16)	<0.01
3 (10)	0.80 (0.65-0.99)	0.25	3 (10)	1.20 (0.98-1.48)	0.04
4 (11)	0.83 (0.70-1.00)	0.62	4 (11)	1.13 (0.98-1.32)	0.26

despite a significant positive association found for current drinking (OR = 1.66 [1.33-2.07]); (ref. 56). The effects of former drinking and cumulative consumption should be investigated to further clarify the etiologic role of alcoholic beverage consumption in lung cancer risk.

A previous meta-analysis found no clear association between total alcohol intake and lung cancer risk, except at a very high level of consumption (50 ~ 80% increase in risk for ≥2,000 grams of ethanol per month or approximately ≥5 drinks per day); (ref. 46). Our results suggest an alternative explanation for the null associations previously observed for total alcohol, i.e., the lack of an obvious association could be due to a mixture of a possible inverse association for wine and positive associations for beer and liquor, especially at moderate levels of consumption. On the other hand, the results from Korte et al. (46) suggest that a J shaped relationship may exist for wine drinking, i.e., with heavy consumption, the potential detrimental effect of ethanol may outweigh the beneficial effects of antioxidants. In our dose-response analysis, a J-shaped curve was not indicated. This may be due to the likelihood that wine drinking is mostly modest in the US and Canada. In Benedetti et al. (30), the mean number of daily drinks of wine among those who drank at least one drink per day was reported to be two for both Canadian men and women. A major limitation in our study was that we could not summarize the effects of heavy drinking for all three types of alcoholic beverages due to the lack of such data in the original studies. We wish to emphasize the presence of this limitation in both the method of dose-specific (categorical) meta-analysis and the dose-response regression. Another limitation of the dose-response curves is poor fit of the models, which is likely due to sparse data for high consumption, lack of reliable average consumption estimates for the open-ended categories, and residual heterogeneity between studies (e.g., potential effect modification by dietary intake and/or tobacco smoking; ref. 11).

It should also be noted that the relative risk estimates for one drink or greater per day reported in this study are averages for those drinking at least one drink per day and do not represent risk estimates for all possible levels of drinking beyond one drink per day. The distribution for drinkers of this category very likely has a long right-tail (44), and our confidence in the results diminish as we move further along the tail to the higher levels of consumption. To properly assess risk associated with higher intake and to advance our knowledge on the causal effect of alcoholic beverage drinking on lung cancer, further studies are needed to examine the association for heavy and extreme consumption of all three types of alcoholic beverages, with careful control for cigarette smoking and other previously mentioned potential confounders.

At present, we were able to identify only two studies that reported risk estimates for higher levels of beer, wine, and liquor drinking (i.e., greater than three drinks per day). Both studies were conducted in Uruguay by De Stefani et al. (32, 33). De Stefani et al. (32, 33) examined the risk associated with daily consumption of >3 drinks of beer, >6 drinks of wine, and >6 drinks of liquor in Uruguayan men. However, whereas the earlier study (32) reported an RR of 3.4 (95% CI, 1.3-15.2), 1.5 (95% CI, 0.9-3.3), and 1.1 (95% CI, 0.6-1.4) for beer, wine, and liquor (Table 1), the later study (33) found an association in the opposite direction for beer (RR, 0.6; 95% CI, 0.3-1.6) and wine (RR, 0.4; 95% CI, 0.2-1.1; Table 1). Although the two studies were conducted in a seemingly similar population, a possible explanation for differences in the results may be the composition of the histologic types of the cancers; the first study composed of predominantly

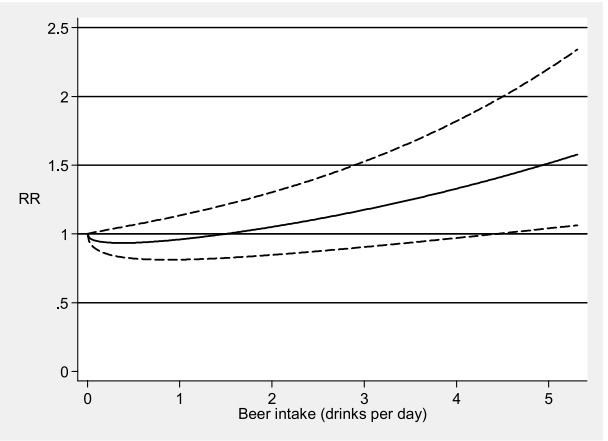

Figure 1. The model-predicted dose-response curve for beer drinking (drinks per day) and 95% CIs (*dashed lines*). The best fitted model included a square root term and a linear term. The regression coefficients (and SEs) on the log RR scale for the terms are −0.2239 (0.1237) and 0.1830 (0.0603), respectively. The regression model was fitted based on a range of beer drinking between 0 and 5.3 drinks per day (derived from the source studies). The goodness-of-fit test suggested the model had poor fit (P value < 0.01).

squamous cell carcinomas with a mix of adenocarcinomas and small cell lung carcinomas, whereas the second study included only adenocarcinomas. In this meta-analysis, we tried to account for this in the meta-regression. Composition of histologic type, however, was not found to contribute greatly to the heterogeneity of results, which may be more of a reflection of the lack of power to detect a difference in effect rather than no actual heterogeneity of effect.

Data on the effects of alcohol use on different histologic types are limited, and they are often derived from small samples. Conflicting findings have been reported for total alcohol use (11). Some studies reported a stronger effect on squamous cell carcinoma (57, 58), whereas others reported a stronger effect on adenocarcinoma (6, 9, 44, 59, 60). However, when considering individual alcoholic beverage, studies have shown little discrepancy of risk among lung cancer cell types (31, 32), although the authors noted that the power to detect potential difference was low. Ideally, histologic types should be analyzed separately with sufficient sample size (which is more feasible with pooled analysis) because different types may have different etiologies.

Although there are several important limitations in interpreting our results, there is also well recognized biological plausibility for these findings. The inverse association of wine over a certain range of consumption, if it is truly causal, may be attributed to its antioxidative compounds, such as flavonoids and resveratrol. Resveratrol has been extensively studied for its potential as a cancer chemopreventive agent. Resveratrol alters the activation process of procarcinogens in human bronchial epithelial cells *in vitro* (61) and retards lung tumor growth in mice (62). However, the effects of resveratrol from dietary sources on human lung carcinogenesis remain to be determined. It should also be noted that the phytochemical contents are different for red wine and white wine. In general, white wine has shown a lower content of resveratrol and antioxidative activity than red wine (17, 63, 64). We identified one study that reported separate effect estimates for red and white wine consumption (21). Although a significant inverse association was observed for red wine (OR, 0.87; 95% CI, 0.77-0.99 per daily glass), the reverse was found for white wine consumption (OR, 1.20; 95% CI, 1.01-1.42 per daily glass; ref. 21). These results suggest that the effects of red wine and white wine consumption on lung cancer risk may be different and should be examined separately in future studies.

Several mechanisms have been proposed for the potential carcinogenic effect of ethanol, including the generation of acetaldehyde and oxidative stress during its metabolism (65). This may account for the associations observed for beer and liquor. Although one standard drink of wine, beer, and liquor contains similar amounts of ethanol, it is possible that the rich antioxidative compounds in wine may counteract the pro-oxidative effect of ethanol, at least at low or moderate levels of consumption (66). It is also possible that the carcinogenic compounds found in beer and liquors, such as nitrosamines and PAHs, may contribute to the increased risk. This hypothesis suggests that the effects of beer and liquors may be different in different countries due to variations in the production processes and regulatory standards. One study reported that the maximum concentration of nitrosamines found in beer varied from 0.5 μg/L in Demark to 68 μg/L in Germany (15). Unfortunately, there are currently insufficient data to examine variations between countries because most studies identified were conducted in the United States or Canada. One study conducted in India found a strong

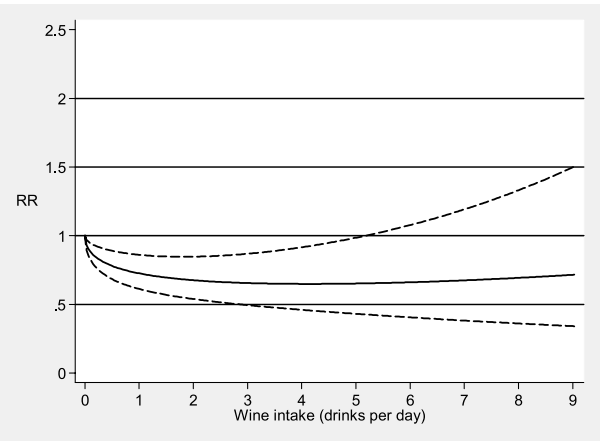

Figure 2. The model-predicted dose-response curve for wine drinking (drinks per day) and 95% CIs (*dashed lines*). The best fitted model included a square root term and a linear term. The regression coefficients (and SEs) on the log RR scale for the terms are −0.4249 (0.1241) and 0.1044 (0.0632), respectively. The regression model was fitted based on a range of wine drinking between 0 and 9.0 drinks per day (derived from the source studies). The goodness-of-fit test suggested the model had poor fit (P value < 0.01).

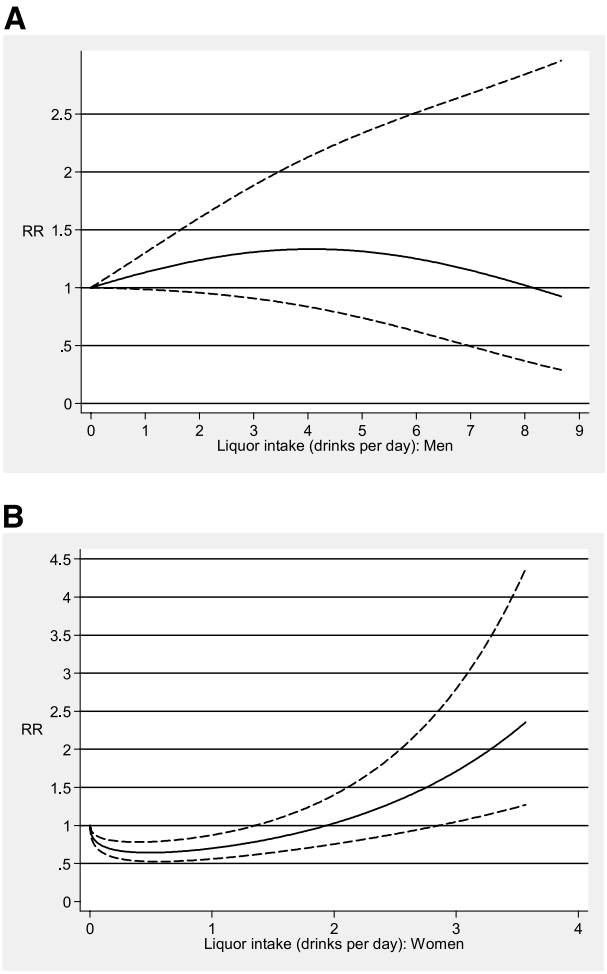

Figure 3. A. The model-predicted dose-response curve for liquor drinking (drink per day) in men and 95% CIs (*dashed lines*). The best fitted model included a linear term and a squared term. The regression coefficients (and SEs) on the log RR scale are 0.1412 (0.0771) and −0.0173 (0.0010), respectively. The regression model was fitted based on a range of liquor drinking between 0 and 8.7 drinks per day (derived from the source studies). The goodness-of-fit test suggested that the model had poor fit (*P* value = 0.01). **B.** The model-predicted dose-response curve for liquor drinking (drink per day) in women and 95% CIs (*dashed lines*). The best fitted model included a square root term and a linear term. The regression coefficients (and SEs) on the log RR scale are −1.2688 (0.2589) and 0.9115 (0.1939), respectively. The regression model was fitted based on a range of liquor drinking between 0 and 3.6 drinks per day (derived from the source studies). The goodness-of-fit test did not detect problems with the model fit (*P* value = 0.13).

association between ever-drinking ''Indian alcohols'' and lung cancer risk among never-smokers (OR, 2.67; 95% CI, 1.02-7.02), where ''Indian alcohols'' were mainly locally produced liquors (56). Furthermore, there is a lack of the literature on studies from countries where beer and/or liquors are heavily used (e.g., Germany and Russia) as well as developing countries.

We are less confident about the inverse association observed for light beer drinking because it was not observed in men and was sensitive to the inclusion of the outlier study in women. It is not clear whether there is a biological mechanism underlying this association, although findings from several studies support a biological plausibility. For example, it is possible that the inverse association is attributed to the antioxidants and selenium found in beer (67). Several studies on laboratory animals suggest that beer inhibits the mutagenicity of heterocyclic amines (a carcinogen found in the human diet) *in vivo* (68-70). In one study, wine, brandy, and Japanese sake also showed the same effect as that of beer *in vitro* (70). At this point, the possibility of residual confounding cannot be excluded. Although it has not been previously reported, it is possible that light beer drinkers may be different from both heavy drinkers and nondrinkers in terms of their general lifestyle and socioeconomic status.

To our knowledge, this is the first meta-analysis that examines the separate effects of beer, wine, and liquor consumption on lung cancer risk. We included both a dose-specific (categorical) meta-analysis and a dose-response meta-regression because both have limitations and, in combination, may provide more information: whereas the dose-specific method allows us to get a fair estimate at lower doses, the regression method allows us to model risk at higher levels of exposure. Our results suggest that different types of alcoholic beverages may have different effects on lung carcinogenesis. However, the possibility that residual confounding may explain these associations cannot be excluded at this point. The results of our meta-analyses indicate that it is necessary to consider the types of alcoholic beverages used when measuring alcohol consumption. Our results also suggest that heavy beer and liquor drinking may have an adverse effect on lung cancer risk. These findings have important implications for countries where beer or liquor is consumed heavily. Our review identified important gaps in the current literature that should be addressed in future studies. First, well-designed epidemiologic studies are needed to determine the risk for high beer/wine/liquor intake and to establish the dose-response relationship. Second, the positive associations observed for beer and liquor as well as the inverse associations for moderate wine drinking need to be investigated further with improved control of confounding and separation of lung cancer histologic type. Lastly, more research examining this public health question needs to be conducted in regions other than North America.

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