

Review

Alcohol Consumption and Lung Cancer: A Review of the Epidemiologic Evidence¹

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Abstract

A role for alcohol consumption in lung cancer etiology has been suggested in some studies, but this possible relationship has been often regarded with skepticism, with any indication of an association being attributed to confounding by cigarette smoking. The purpose of this work was to review the epidemiological evidence for an association of alcohol and lung cancer and to identify gaps in that research. The studies reviewed here provide some indication that alcohol and particularly beer intake may increase lung cancer risk after controlling for cigarette smoking. Although the evidence is not conclusive, it warrants additional consideration of alcohol as a risk factor in lung cancer etiology, independent of cigarette smoking. Recommendations for future studies are provided.

Introduction

Lung cancer is the leading cause of cancer deaths in men and women in the United States (1). The role of cigarette smoking in lung cancer etiology is well accepted, but it does not explain all of the variance in disease distribution. Alcohol, particularly beer intake, was first proposed as a possible risk factor for lung cancer by Potter and McMichael (2) in a review of the literature in 1984. Since then, alcohol consumption has been suggested to increase lung cancer risk in a number of studies, but in general, its involvement in lung cancer etiology has been regarded with skepticism, with any indication of an association being attributed in most instances to confounding by cigarette smoking. It is indeed difficult to disentangle the effects of alcohol and smoking because the two exposures tend to be correlated, but this problem does not automatically negate the possibility of an alcohol effect. The possible role of alcohol intake is of particular importance in lung cancer prevention because it is a modifiable behavior. Furthermore, the interaction of alcohol with cigarette smoking and dietary intake may be of relevance. A

panel of experts commissioned by the World Cancer Research Fund and the American Institute for Cancer Research, after reviewing the epidemiological evidence, concluded in 1997 that alcohol intake may “possibly” increase lung cancer risk (3). We conducted a comprehensive review to evaluate the current epidemiological evidence regarding alcohol consumption as a risk factor in lung cancer etiology and to identify gaps in that research.

Materials and Methods

In preparing this review we followed published guidelines for review papers (4–7). Our literature search was limited to English-language, peer-reviewed publications. Studies were identified mainly through electronic searches on Medline (1966–2000) complemented with manual searches of references in other published articles. An additional search on CancerLit (1983–2000) did not reveal other relevant articles.

Only case-control and prospective studies directly evaluating the relationship between primary lung cancer and alcohol using collected alcohol data (as opposed to studies that speculated about alcohol consumption of a particular group) were included in this review. Our Medline search revealed 27 relevant articles (8–34), and seven additional articles (35–41) were identified through manual searches of published reference lists. After careful review of the 34 identified articles, eight case-control studies (8, 14, 17, 21, 25, 26, 35, 36) and two prospective studies (23, 39) were excluded for not presenting smoking-adjusted risk estimates.

In this review we used qualitative methods to summarize the data. The criteria to assess the quality of the studies were assessment of alcohol exposure, sample size, choice of comparison group, and particularly possible residual confounding by cigarette smoking. The conclusions of this review are based on our subjective interpretation of the available epidemiological evidence of a relationship between alcohol consumption and lung cancer.

Results

Epidemiologic Studies

Total Alcohol. Four (20, 24, 29, 37) of the eight case-control studies (10, 15, 16, 20, 24, 29, 31, 37) evaluating the effect of total alcohol consumption reported an association (Table 1). In one of these studies the relationship was limited to heavy smokers (20), but there was also a suggestion of an association for female never-smokers in another study (37). Two of the negative studies (16, 31) combined males and females and adjusted for gender. Pierce *et al.* (15) also did not find an association with the number of drinks/week or the number of years drinking, both as continuous variables. This study included only 71 cases and 71 hospital controls, all with a high prevalence of smoking and alcohol intake, according to the authors. The fourth negative study was also small and hospital-based and did not include much information on how the hy-

Received 12/15/98; revised 3/29/01; accepted 4/9/01.

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¹ This work was supported in part by National Cancer Institute Grant CA11535, National Institute on Alcohol Abuse and Alcoholism Grant AA09802, and (to J. E. V.) Fogarty International Center Grant 1F06TW02223-01.

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Table 1 Results reported by studies evaluating the effect of total alcohol consumption on lung cancer risk

| Study and location | Study size ^a and location | Smoking adjustment | Comparison | OR/RR (95% CI or P) |
|--|---|---|--|---|
| Case control studies | | | | |
| Kabat and Wynder, 1984 (10) | 37/37 M 97/97 F (U.S.) | NA ^b (Never smokers) | No difference in alcohol consumption found | Not presented |
| Koo, 1988 (37) | 88/137 F (China) | NA (Never smokers) | Drinking ≥ 1 times/wk (yes/no) | 1.8 (0.9–3.7) |
| Restrepo <i>et al.</i> , 1989 (16) | 102/181 M and F (Colombia) | Cigarettes/day | Nondrinker Former drinker Occasional drinker Habitual drinker | 1.0 0.6 ($P > 0.05$) 0.9 ($P > 0.05$) 1.1 ($P > 0.05$) |
| Pierce <i>et al.</i> , 1989 (15) | 71/71 M (Australia) | “Smoking pattern” (smoking prevalence, time since cessation of smoking and cigarettes/day) | Drinks/wk (continuous variable) Duration, yr (continuous variable) | 1.0 (0.99–1.01) 1.0 (0.96, 1.03) |
| Bandera <i>et al.</i> , 1992 (20) | 280/564 white M (U.S.) | Smoking history (pack-yr) | >22 drinks/mo vs. drinking less | (>40 pack-yr cigarette smoking) 1.6 (1.0–2.5) (No association for light smokers) |
| De Stefani <i>et al.</i> , 1993 (24) | 327/350 M (Uruguay) | Pack-yr in four categories | Nondrinker vs. ml of pure ethanol/day ^c 1–60 ml 61–176 >176 | 1.4 (0.9–2.0) 1.6 (0.9–2.0) 2.2 (1.3–3.0) P for trend: 0.002 |
| Dosemeci <i>et al.</i> , 1997 (29) | 1,210/829 M (Turkey) | Smoking categories (never, <20 pack-yr, 20–29 pack-yr, >29 pack-yr) | vs. nondrinker Amount (cl/wk) 1–35 36–140 >141 | 1.6 (0.8–2.9) 1.7 (1.1–2.7) 1.7 (1.7–2.9) P for trend <0.001 |
| Carpenter <i>et al.</i> , 1998 (31) | 261/615 M and F (U.S.) | Indicator variables for pack-yr and yr since quitting smoking | Never-3 drinks/mo vs. >3 drinks/day | 1.1 (0.5–2.4) |
| Cohort studies | | | | |
| Kvale <i>et al.</i> , 1983 (9) | 116/10,602 M 11.5 follow-up (Norway) | Never-, ex- and current smokers of 1–9, 10–19, and ≥ 20 cigarettes/day | Highest tertile of alcohol consumption vs. lowest | All subjects: 1.3 ($P = 0.37$) Low vitamin A consumers: 3.6 ($P = 0.03$) |
| Gordon and Kannel, 1984 (40) | 42/2,106 M 9/2,641 F 22 yr follow-up (Framingham Study, U.S.) | Cigarettes/day | oz/mo as continuous variable | 1.0 ($P > 0.05$) M 0.7 ($P > 0.05$) F |
| Pollack <i>et al.</i> , 1984 (11) | 89/7,837 M 14-yr follow-up (Japan-Hawaii Cancer Study, Hawaii) | Smoking status Adjustment for amount smoked did not change estimates | (oz/mo based on usual consumption during 1 mo at baseline) None <5 5–14 15–39 >39 (or >1.18 l/mo) | (CI or P not shown) 1.0 0.7 1.3 1.7 1.9 P for trend: 0.003 |
| Kono <i>et al.</i> , 1986, 1987 (12, 41) | 74/5,477 M 19-yr follow-up (Japanese Physicians Study, Japan) | Non, ex- and current smokers of <10 , 10–19, ≥ 20 cigarettes day | Nondrinker Ex-drinker Occasional drinker Daily drinker of <54 ml of alcohol ≥ 54 ml of alcohol | 1.0 0.6 (0.2–1.5) 0.4 (0.2–0.8) 0.8 (0.4–1.4) 0.9 (0.5–1.7) |
| Stemmermann <i>et al.</i> , 1990 (18) | 209/8,006 M 22-yr follow-up (Japan-Hawaii Cancer Study, Hawaii) | Current smoking status, age started smoking and no. of cigarettes/day (current smokers), ex-smoker status, maximum no. of cigarettes/day and yr smoking maximum amount (ex-smokers) | (oz/mo based on 24-h recall) 0 <5 5–14 15–39 >39 | 1.0 0.7 (0.5–1.2) 0.9 (0.6–1.5) 1.4 (1.0–2.1) 1.1 (0.7–1.6) P for trend 0.09 |
| Bandera <i>et al.</i> , 1997 (28) | 395/27,544 M 130/20,456 F 8 yr (New York State Cohort Study, U.S.) | Cigarettes/day and yr smoking | Highest vs. lowest tertile of consumption | 1.1 (0.9–1.4) M P for trend: 0.001 1.0 (0.6–1.6) F P for trend: 0.8 (Squamous cell carcinoma cases) 1.5 (0.97–2.3) |

Table 1 Continued

| Study and location | Study size ^b and location | Smoking adjustment | Comparison | OR/RR (95% CI or P) |
|------------------------------------|--|---|---|--|
| Cohort studies (cont'd) | | | | |
| Prescott <i>et al.</i> , 1999 (32) | 480/15,107 M 194/13,053 F (Copenhagen City Heart Study, the Centre of Preventive Medicine, and the Copenhagen Male Study, Denmark) | Six categories of present smoking and eight categories of duration of smoking (Best fit based on likelihood ratio test) | No. of drinks/wk: <1 1–6 7–13 14–20 21–41 >41 | (M) 1.0 0.8 (0.6–1.2) 1.0 (0.7–1.4) 0.9 (0.6–1.3) 1.2 (0.9–1.7) 1.6 (1.1–2.3) P for trend: 0.002 (No relationship for F) |
| Woodson <i>et al.</i> , 1999 (33) | 1059/27,111 M smokers 7.7 yr (ATBC Study, Finland) | Cigarettes smoked per day and total yr smoked | Nondrinker vs. drinker Highest quartile of drinking vs. lowest quartile of g/day) | 1.2 (0.9–1.4) 1.0 (0.8–1.2) (Adenocarcinoma) 1.7 (1.0–2.8) |
| Breslow <i>et al.</i> , 2000 (34) | 158/20,004 M and F 8.5 yr (U.S.) | Packs/day and duration of smoking as continuous variables | Highest quartile of alcohol intake compared with lowest | 1.3 (0.8–2.0) (Nonsmokers) 2.3 (1.1–4.6) |

^a Study size refers to no. of cases and controls in case-control studies and no. of cases and total subjects in cohort studies.

^b NA, not applicable.

^c Beer: 60 ml of pure ethanol/liter; wine: 120 ml/liter; hard liquor: 460 ml/liter.

pothesis was tested (10). In general, the negative studies tended to include fewer cases than the positive studies.

Results from cohort studies have not been very consistent regarding alcohol as a risk factor for lung cancer. The strongest support for the hypothesis came from a study by Pollack *et al.* (11) using data from the Japan-Hawaii Cancer Study. Alcohol consumption was ascertained by asking participants to report their usual consumption of wine (including Japanese sake and fortified wines), beer, and whiskey (including other hard liquor) during 1 month. A dose-response relationship between lung cancer incidence and alcohol consumed in oz/month ($P = 0.003$) was observed, taking into account age at examination and cigarette smoking status. Those in the highest category of consumption (40+ oz/month) had 1.9 times higher lung cancer incidence than nondrinkers. Similar results were obtained when categories of the number of cigarettes smoked, for current smokers, were added to the model. These results were not replicated in a second report from the same study (18), which used a different method to ascertain alcohol intake, the 24-h recall. In that there tends to be considerable intra-individual variability in alcohol consumption, large random misclassification of exposure with the 24-h recall likely biased results toward the null. It should be noted here that this latter study (18) included >double the number of lung cancer cases as the former study (11) and extended the follow-up by 8 years, which may also explain the different results.

A more recent study conducted in Denmark also found an association with total alcohol intake (P for trend: 0.002) among males after carefully adjusting for cigarette smoking (32). However, risk estimates were elevated only for heavy drinkers, those consuming >41 drinks/week (RR:³ 1.57; 95% CI: 1.06, 2.33).

Other prospective studies have reported an association with total alcohol restricted to selected groups, such as subjects with low intake of vitamin A (9), squamous cell carcinoma cases (28), adenocarcinoma cases (33), and nonsmokers (34). The remaining two cohort studies, the Framingham Study (40) and the Japanese Physician Study (12, 41), did not provide evidence of an association between total alcohol consumption

and lung cancer mortality. These two cohort studies were based on very small number of lung cancer deaths and had long follow-up periods. Furthermore, in the Framingham Study (40), the effect of alcohol was only evaluated as a continuous variable.

A significant dose-response relationship with total alcohol intake has been reported in two case-control studies (24, 29) and three cohort studies (11, 28, 32). The studies that reported an association found risk estimates ranging from 1.6 for >41 drinks/week to 2.2 for >176 ml of pure ethanol/day (almost 3 liters of beer/day).

Alcoholic Beverage Type

Beer. Studies evaluating the alcohol effect on lung cancer by beverage type reported more frequently a relationship with beer and liquor than with wine (Tables 2 and 3). Of the 11 studies evaluating the effect of beer (11, 13, 19, 20, 22, 24, 27, 31–33, 38), 3 case-control (20, 24, 27) and 2 cohort studies (22, 32) reported a positive association, 2 studies offered weak support for a relationship (13, 19), and 4 did not find an association (11, 31, 33, 38).

In the Western New York Diet Study (20) and a nested case-control within the Iowa Women's Health Study (22), whereas there was no association with wine and liquor, beer drinkers were at increased risk. These two studies reported similar risk for a similar level of exposure. In the former study (20), there was approximately a doubling of risk for men consuming more than 40 beers/month, compared with nondrinkers of beer, with ORs adjusted for age, education, pack-years of cigarette smoking, carotenoid intake, and fat intake. In the Iowa Women's Health Study (22) the smoking-adjusted OR (six categories of pack-years) for women drinking ≥ 1 beer/day was 1.9 (95% CI: 0.96–3.9) compared with nondrinkers. An additional cohort study conducted in Denmark (32) reported a RR of 1.4 for those drinking >13 beers/week compared with those drinking <1 beer/week.

A significant dose-response relationship has been reported by Bandera *et al.* (20) and De Stefani *et al.* (24). In this latter study, conducted in Uruguay (24), those consuming >1 liter of beer/day had an OR of 3.4 (95% CI: 1.3–15.2), compared with nondrinkers. Analyses were adjusted for pack-years in four categories, age in four levels, residence in two categories, and

³ The abbreviations used are: RR, relative risk; CI, confidence interval; OR, odds ratio; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.

Table 2 Results reported by case-control studies evaluating the effect of alcoholic beverages on lung cancer risk^a

| Study | Comparison | Beer | Comparison | Wine | Comparison | Liquor | Comments |
|---|--|--|---|---|--|--|--|
| Mettlin, 1989 (U.S.) (13) | Never <1 time/wk 4–9 times/wk 10+ times/wk | 1.0 0.5 (0.3–0.8) 0.7 (0.4–1.2) 1.3 (0.8–2.1) | (same) | 1.0 0.5 (0.4–0.8) 0.8 (0.4–1.5) 0.9 (0.4–2.5) | (same) | 1.0 0.7 (0.5–1.0) 0.6 (0.4–0.9) 0.6 (0.4–1.1) | M and F combined adjusted for sex, pack-yr and other factors |
| Bandera <i>et al.</i> , 1992 (U.S.) (20) | 40+ vs. 0 beers/mo | 1.9 (1.1–3.4) <i>P</i> for trend <0.01 | 2+ vs. 0 drinks/mo | 0.7 (0.5–1.1) <i>P</i> for trend 0.4 | 9+ vs. 0 drinks/mo | 1.1 (0.7–1.6) <i>P</i> for trend 0.1 | White M |
| De Stefani <i>et al.</i> , 1993 (Uruguay) (24) | (ml of pure ethanol/day) Nondrinker 1–9 10–59 60+ (1 l. of beer/day) | 1.0 0.7 (0.3–2.5) 1.4 (0.4–6.2) 3.4 (1.3–15.2) <i>P</i> for trend 0.02 | (ml of pure ethanol/day) Nondrinker 1–36 37–120 121+ (1 liter of wine/day) | 1.0 1.2 (0.7–2.2) 1.3 (0.7–3.1) 1.5 (0.9–3.3) <i>P</i> for trend 0.09 | (ml of pure ethanol/day) Nondrinker 1–34 35–115 116+ (.25 l. liquor/day) | 1.0 0.9 (0.6–1.6) 1.3 (0.8–2.6) 1.1 (0.6–1.4) <i>P</i> for trend 0.5 | M |
| Mayne <i>et al.</i> , 1994 (U.S.) (38) | Highest quartile compared with lowest | 1.2 (CI not presented, includes one) <i>P</i> for trend >0.05 | | Not presented | | Not presented | Nonsmokers Adjusted for prior cigarette use. M and F combined, not adjusted for sex |
| De Stefani <i>et al.</i> , 1996 (Uruguay) (27) | Drinkers vs. never- drinkers of beer and liquor | 1.9 (0.96–3.7) | | Not presented | (same) | 1.4 (0.98–2.1) | M + F combined adjusted for sex, pack-yr and other factors |
| Rachtan <i>et al.</i> , 1997 (Poland) (30) | | Adjusted OR not presented | | Adjusted OR not presented | Nondrinker 1–2 times/mo 1+ times/mo | 1.0 2.6 (1.2–5.5) 7.5 (0.8–71.0) <i>P</i> for trend 0.003 | F Adjusted for pack-yr and carrot consumption |
| Carpenter <i>et al.</i> , 1998 (U.S.) (31) | Never-3 drinks/mo 1–6 drinks/wk 1+ drinks/day | 1.0 0.3 (0.2–0.7) 0.9 (0.4–1.7) <i>P</i> for trend 0.45 | (same) | 1.0 0.7 (0.4–1.3) 0.8 (0.3–1.9) <i>P</i> for trend 0.66 | (same) | 1.0 1.2 (0.7–2.2) 1.9 (1.0–3.4) <i>P</i> for trend 0.06 | M + F adjusted for sex |

^a Smoking-adjusted ORs and their 95% CIs.

other types of alcoholic beverages. These results were replicated in a different study conducted by the same investigators 3 years later (27), which found that drinking beer (yes/never) was associated with an increased lung cancer (smoking-adjusted OR: 1.89; 95% CI: 0.96–3.73).

Hard Liquor. Five (11, 27, 30–32) of the 11 studies evaluating the effect of hard liquor (11, 13, 19, 20, 22, 24, 27, 30–33) reported a positive association with lung cancer risk (Tables 2 and 3). Also, a study by Chow *et al.* (19) found an elevated risk limited to ex-drinkers of hard liquor with an OR of 1.9 (95% CI: 1.1–3.1). The strength of the relationship with hard liquor has been reported to be from a RR of 1.5 (0.99–2.1) for consuming >13 drinks/week (32) to a RR of 2.6 (*P* < 0.01; CI not reported) for those having >1.5 liters of liquor/month (11). A significant dose-response relationship has also been reported (30).

Wine. To our knowledge, only eight studies evaluating the effect of wine consumption on lung cancer risk have been published in the peer-reviewed literature (Refs. 11, 13, 20, 22, 24, 31–33; Tables 2 and 3). Two studies conducted in Uruguay (24) and Hawaii (11) reported a positive association with wine intake. In contrast, Prescott *et al.* (32) found an inverse relationship among males, with those consuming >13 drinks of wine/month having a RR of 0.4 (95% CI: 0.2–0.86). Four additional studies (13, 20, 31, 33) reported RRs <1 for wine drinkers, but risk estimates did not reach statistical significance.

Studies conducted in the United States were confronted with a low prevalence of wine drinking, resulting in small numbers of both cases and controls in the highest category of intake (13, 31) or a very low cutoff point for the highest category of wine intake (20). One possible explanation for these contradictory results is that wine may be protective up to a certain level where the potential antioxidant effects of wine are outweighed by the detrimental effects of high levels of ethanol exposure. The two positive studies mentioned previously support this theory. The study conducted in Hawaii suggested a U-shaped relationship (11), and in the study conducted in Uruguay (24) about one-third of the cases drank >1 liter of wine/day. It should also be noted that studies have found wine to be less correlated with cigarette smoking than any other type of alcohol (20, 31, 32).

Relevant Exposure Period. Because the possible latent period between exposure to alcohol and the development of lung cancer is unknown, it is uncertain whether the relevant parameter to evaluate is recent, past, or cumulative lifetime drinking. Potter *et al.* (22) have suggested that alcohol and beer may act in the later stages of carcinogenesis. Moreover, experimental studies have generally indicated that ethanol acts as a tumor promoter, not as initiator (42). On the basis of these findings, current drinking appears to be the important factor to examine. On the other hand, if the effect of alcohol on the lung is cumulative, assessing recent intake exclusively may lead to an underestimation of the association. Studies have typically as-

Table 3 Results reported by prospective studies evaluating the effect of alcoholic beverages on lung cancer risk^a

| Study | Comparison | Beer | Comparison | Wine | Comparison | Liquor | Comments |
|--|--|--|--|---|--|--|---|
| Pollack <i>et al.</i> , 1984 (Hawaii) (11) | No relationship with beer. RRs not presented | | >1.5 liters of wine/mo vs. not drinking wine | 2.2 ($P = 0.03$) | >1.5 liters of liquor/mo vs. not drinking liquor | 2.6 ($P < 0.01$) | Japanese men |
| Chow <i>et al.</i> , 1992 (U.S.) (19) | Never used <3 times/mo 3–5 6–13 >13 Used before | 1.0 1.2 (0.8–1.9) 1.4 (0.8–2.3) 1.7 (1.0–2.9) 1.1 (0.6–1.9) 1.8 (1.1–3.0) | | Not evaluated | (same) | 1.0 1.3 (0.9–2.0) 1.3 (0.8–2.1) 1.3 (0.7–2.2) 1.0 (0.5–1.8) 1.9 (1.1–3.1) | White M. Adjusted for never, other tobacco only, occasional/past daily use or current daily use of 1–19, 20–29, 30+ cigarettes) Mortality study. 20 yr of follow-up. Ex-drinkers did not smoke more than current drinkers |
| Potter <i>et al.</i> , 1992 (U.S.) (22) | None <1 beer/day 1+ beers/day | 1.0 0.6 (0.3–1.2) 1.9 (0.96–3.9) | Consumption was similar for cases and controls | | 1+ drinks/day vs. none | 1.1 (0.6–2.3) | Nested case-control study within the Iowa Women's Health Study. Adjusted for six categories of pack-yr |
| Prescott <i>et al.</i> , 1999 (Denmark) (32) | <1/wk 1–13 13+ | 1.0 1.1 (0.8–1.4) 1.4 (1.0–1.8) | (same) | 1.0 0.8 (0.6–0.97) 0.4 (0.2–0.86) | (same) | 1.0 1.2 (0.97–1.5) 1.5 (0.99–2.1) | RRs presented here are for M. Analyses in F were based in small number of cases |
| Woodson <i>et al.</i> , 1999 (Finland) (33) | Highest (>11.6 g/day) vs. lowest quartile (0.01–1.6 g/day) | 0.9 (0.7–1.1) P for trend 0.19 | High (2.1–67.5 g/day) vs. low (0.09–2) | 0.8 (0.6–1.1) P for trend 0.02 | Highest (>22.8 g/day) vs. lowest quartile (0.01–2.6 g/day) | 1.1 (0.9–1.3) P for trend 0.12 | M heavy smokers |

^a Smoking-adjusted RR and their 95% CIs. For method of adjusting for smoking see Table 1 or comments in this table if study is not listed in Table 1.

certained recent intake, and two case-control studies (15, 29) and one cohort study (28) evaluated the number of years drinking. These three studies found similar risk estimates for the duration of drinking and amount of alcohol consumed. Also, Carpenter *et al.* (31) found similar effects for recent and past alcohol intake between ages 30–40 years. To our knowledge, the effect of a cumulative alcohol index based on a detailed lifetime drinking history has not been evaluated thus far.

Effect by Smoking Status. Given the difficulties in separating the effects of alcohol and smoking on lung cancer, the best way of demonstrating an independent alcohol effect is examining the relationship between alcohol and lung cancer among never-smokers. However, the incidence of the disease in this group is so low that it is difficult to accrue sufficient cases to evaluate the association. To our knowledge only two case-control studies examined the effect of alcohol among never-smokers (10, 37). The first study (10) was hospital-based, conducted among subjects who never smoked on a regular basis, defined as never smoking as much as one cigarette, pipe, or cigar per day for 1 year. No significant differences in alcohol intake between cases and controls were found for males (37 cases, 37 controls) or females (97 cases, 97 controls). The second study (37) was conducted among Chinese women who never smoked, defined as those smoking <20 cigarettes or pipes in the past. Participants (88 cases and 137 controls) consuming any type of alcohol ≥ 1 time/week had an OR of 1.85 (95% CI: 0.93–3.70; P for trend: 0.08), compared with those drinking less often, adjusted for age, number of live birth, and schooling. In that smoking may be less accepted among Chinese women than in other cultures, it is possible that subjects underreported their smoking habits, leading to residual confounding by smoking and an overestimation of the OR. However, alcohol intake has

also a social stigma in this culture, which may have led to underreporting of alcohol consumption, especially at high levels and consequently, to an underestimation of the risk estimate for the highest category.

One additional population-based case-control study was conducted among nonsmokers, of which 55.9% of cases and controls were former smokers (38). Participants (201 female cases and 212 male cases and same number of controls) had either never smoked >100 cigarettes or had smoked at some time but <100 cigarettes in the 10 years prior to diagnosis. There was no indication of an association with beer intake after adjusting for prior cigarette use.

Other studies including both nonsmokers and smokers have attempted to stratify by smoking, but the number of lung cancers among never or nonsmokers was too small to evaluate the association with alcohol separately for them (20, 24, 28, 31, 32). A recent prospective study (34) reported an increased risk of lung cancer mortality among nonsmokers with a RR of 2.3 (95% CI: 1.1–4.6) for the highest compared with the lowest quartile of alcohol intake. The authors do not specify whether nonsmokers include former smokers and, if so, whether analyses were adjusted for prior cigarette use. There was some indication of a stronger relationship with total alcohol among heavy smokers after adjusting for cigarette smoking in a case-control (20) and a cohort study (28). Also, Carpenter *et al.* (31) found the relationship between hard liquor consumption and lung cancer to be somewhat stronger for heavy smokers.

Effect by Gender and Race. Lung cancer rates are considerably higher in black males than in white males and slightly higher in black females than in white females (43). Also, it has been reported that, given the same level of smoking, risk estimates are higher for women than for men (43, 44) and for

blacks than for whites (43). The causes for this apparently increased susceptibility are unknown. For these reasons, examining the effect of alcohol consumption by gender and race is of great importance.

Unfortunately, studies of alcohol and lung cancer by gender have not offered conclusive results. Of 14 studies examining the relationship separately in males (9–11, 15, 18–20, 24, 28, 29, 32, 33, 40, 41), 8 reported some indication of an association (9, 11, 19, 20, 24, 28, 29, 32), whereas the remaining 6 found no association. Six studies evaluated the effect for females (10, 22, 28, 32, 37, 40), and only two (22, 37) reported an effect for them. None of these studies compared the strength of the association by gender at the same levels of alcohol consumption. The effect by race has not been evaluated.

Effect by Histological Type. The few studies that examined the relationship with alcohol by cell type were based on a very small numbers and, therefore, the reported differences may have occurred just by chance. In the New York State Cohort (28) there was some indication of an association with alcohol after adjusting for cigarette smoking, years smoking, and other variables only when analyses were restricted to squamous cell carcinoma cases in males. The RR for the third tertile of alcohol consumption in drinks/month compared with the first was 1.49 (95% CI: 0.97–2.31; *P* for trend: 0.0003). The RR for adenocarcinoma was 0.98 (95% CI: 0.61–1.60; *P* for trend: 0.57). There was also a suggestion of a stronger relationship for squamous cell and small cell carcinomas combined in a case-control study among Chinese females, all never-smokers (37). The ORs for drinking alcohol ≥ 1 time/week compared with drinking less were 2.07 (*P* > 0.10; *P* for trend: 0.14; based on 12 cases and 29 controls) for squamous cell and small cell carcinomas and 1.41 (*P* > 0.10; *P* for trend: 0.46; 12 cases and 29 controls) for adenocarcinoma and large cell. However, these findings were based on a very small number of cases and were not statistically significant.

In contrast, a case-control study among men in Uruguay (24) found increased risk of lung cancer for above-median beer consumption for all of the cell types but slightly higher risk estimates for adenocarcinoma for hard liquor and total alcohol. Also, the ATBC Study among male heavy smokers found an increased risk of lung cancer only for adenocarcinoma cases, with a RR of 1.7 (95% CI: 1.0–2.8) for the highest compared with the lowest quartile of intake (45). A case-control study among men in Turkey (29) reported similar risk estimates for squamous cell carcinoma and other cell types combined (including adenocarcinoma and large cell), associated with the amount of alcohol drank per week.

Interaction with Dietary Factors. The few studies that examined the relationship with alcohol by levels of vitamin A, carotenoids, or vegetable consumption found fairly consistently a stronger association for those in the lower category of consumption. Kvåle *et al.* (9) found a relationship between alcohol and lung cancer only among subjects in the lowest tertile of vitamin A consumption after adjusting for age, cigarette smoking, region, urban/rural residence, and socioeconomic group. For the highest tertile of alcohol intake, compared with the lowest, RRs were 3.66 (*P* = 0.03) and 0.21 (*P* = 0.16) for low and high vitamin A intakes, respectively (95% CIs not shown). Also, the protective effect suggested in this study for higher intakes of vitamin A was limited to those with higher alcohol intakes. The test for linear interaction between alcohol and the vitamin A index was significant (*P* = 0.02). In the Western New York Diet Study (20), the relationship found with alcohol was slightly stronger among low carotenoid consumers, but the

confidence limits around the estimates for high and low carotenoid consumers included the null value and overlapped. In the study by De Stefani *et al.* (24) among men in Uruguay, only beer drinkers consuming vegetables ≤ 2 times/week were at increased risk of lung cancer (age- and smoking-adjusted OR: 2.1; 95% CI: 1.0–4.1). The OR for those consuming vegetables more often was 1.1 (95% CI: 0.6–2.1).

Additional support for an effect modification by vitamin A comes from a few studies evaluating the effect of diet or vitamin supplement use on lung cancer risk. These studies examined the role of alcohol only as an effect modifier. A case-control study in Polish men (46) reported higher risk estimates for low consumers of carrots, green vegetables, and boiled vegetables when analyses were restricted to those who drank vodka at levels above average. However, these analyses were based on a very small number of subjects. It is also worth mentioning that the excess risk of lung cancer associated with vitamin supplementation, including β -carotene, found in two chemoprevention trials, the β -Carotene and Retinol Efficacy Trial (47) and the ATBC (45), seemed to be stronger for those in the highest category of alcohol intake. A recent report of the ATBC Study (33), evaluating the relationship between alcohol and lung cancer among trial participants, however, failed to find an interaction between alcohol and dietary vitamin C, vitamin E, and folate, and serum β -carotene, α -tocopherol, and retinol. Also, there was no indication of an interaction between carotenoids and alcohol drinking in the New York State Cohort Study (28).

Possible Biological Mechanisms. The mechanisms by which alcohol may increase lung cancer risk are not known, but several causal pathways have been proposed. Ethanol may increase lung cancer risk through its primary oxidative metabolite, acetaldehyde, a known carcinogen in experimental animals (48). In support of this possible mechanism, Fang and Vaca (49) found elevated DNA adducts of acetaldehyde in peripheral blood cells among alcoholics. Ethanol can also generate oxygen-free radicals through its oxidative metabolism, which can react with cell lipids to produce lipid peroxides (42). Nachiappan *et al.* (42) found increased lipid peroxidation associated with ethanol consumption in the lungs of rats exposed to tobacco-specific nitrosamines. Also, elevated microsomal cytochrome p450 and microsomal enzyme activity have been observed with chronic ethanol consumption, enhancing the activation of procarcinogens and mutagens (50). Impaired DNA repair was also observed among alcohol-fed rats with DNA damage induced by carcinogens (51). Moreover, increased chromosome aberrations have been observed among alcoholics (52).

Besides the apparent effects of alcohol on the lung, alcohol may increase lung carcinogenesis by interacting with cigarette smoking. Several mechanisms have been proposed to explain this interaction: alcohol may act as a solvent of tobacco carcinogens (53), it may change the oxidative capacity of liver microsomes leading to a reduced ability to metabolize tobacco carcinogens (54), or it may affect cellular metabolism resulting in an increased metabolic activation of procarcinogens (54, 55). Finally, excessive alcohol consumption has been associated with nutritional deficiencies, which are immunosuppressive (56).

In addition to ethanol, alcoholic beverages contain other substances with carcinogenic potential such as polycyclic aromatic hydrocarbons from grain roasting, nitrosamines, and asbestos fibers from beer filters (57), as well as tannins, urethan, and arsenic pesticide residues (48), which may also play a role in lung carcinogenesis.

In conclusion, the mechanisms by which alcohol consumption may increase cancer risk are unknown, but several

hypotheses have been proposed, many of which have been substantiated in animal models. Overall, experimental studies indicate that alcohol does not initiate cancer but may potentiate the effect of certain carcinogens by a number of not mutually exclusive mechanisms, including facilitation of cellular entry of carcinogens and/or affecting their metabolism, inhibition of DNA repair, and tumor promotion (58). Although the experimental evidence is not conclusive, it provides some support to the epidemiological research suggesting an increased lung cancer risk associated with alcohol consumption.

Discussion

There is an increasing body of literature suggesting that alcoholic beverages may increase lung cancer risk, after controlling for cigarette smoking. The effect by alcoholic beverage type is not clear, but studies seem to indicate that beer and liquor may increase risk, whereas moderate wine consumption may be protective. The evidence is not compelling though, because studies have often presented conflicting results. As discussed by Willett (59), exceptions to the criteria traditionally used to evaluate causality (consistency, strength of the association, dose-response, temporality, biological plausibility) are common in nutritional epidemiology. For instance, absolute consistency of findings is an unrealistic expectation and should not be used as a criterion to rule out the possibility of a causal relationship (59). The inconsistencies in results among studies may have derived from methodological issues such as incomplete alcohol assessment most likely resulting in substantial random misclassification of exposure (explained in more detail below) and inadequate choice of comparison group or power to detect an association because of small numbers. Moreover, adjustment for confounding variables varied greatly from one study to another. Although all of the studies included here considered cigarette smoking as a confounder of this association, it was controlled for in different ways, undoubtedly resulting in varying degrees of residual confounding by smoking.

The difficulties of assessing alcohol intake are well known. There is a tendency for individuals to underreport their alcohol intake (60), which seems to be more pronounced among heavy drinkers (61) and may differ across populations according to the social acceptance of consuming alcohol (52). Studies of alcohol and lung cancer have varied considerably in their efforts to ascertain alcohol consumption. In some, only drinking status or frequency of intake of any type of alcohol was obtained, whereas others asked about frequency and quantity of consumption of each type of alcoholic beverage. This last approach seems to be the best in that it may improve the recall and report of total drinking and allows for the evaluation of the effect of drinking wine, beer, and liquor. Also, queries limited to the frequency of consumption may result in misclassification because a person drinking infrequently but heavily in those occasions may be classified as light drinker. Furthermore, as mentioned above, it is unclear what the relevant time period is for assessment, whether recent drinking or drinking history is of significance. For all of these reasons, misclassification may have occurred in all of the studies evaluating the relationship between alcohol and lung cancer, in varying degrees, which may also explain the inconsistent findings.

Another possible explanation for the contradictory findings could be the different distribution of type of alcoholic beverages consumed across populations. For instance, in the United States wine may not appear to increase lung cancer risk just because its consumption is lower and less variable than that of beer. In turn, an increased risk is observed with beer consumption, which is the

most common alcoholic beverage consumed in the United States (62). Also, in addition to ethanol, alcoholic beverages contain antioxidants, such as sulfites (63), flavonoids (64), and resveratrol (65; primarily wine) as well as some chemicals with carcinogenic potential such as nitrosamines, asbestos fibers, and polycyclic aromatic hydrocarbons (52; primarily beer). The concentration of these chemicals varies among the different types of alcoholic beverages. For instance, beer, which has more frequently been reported to be associated with lung cancer than wine and hard liquor, has much higher levels of nitrosamines than any other alcoholic beverage (66). These chemicals are formed during the process of production of the different alcoholic beverages. Because production techniques vary over time, different levels of these chemicals over time and in different geographical areas can be anticipated. This could explain, at least partly, some of the discrepant results when comparing epidemiological investigations of this relationship.

Another criterion to evaluate causality is the strength of the association. Comparing and summarizing risk estimates across studies is difficult, however, because of the different methods used to assess and express alcohol intake (3). Moreover, estimates of intake derived from food frequency questionnaires are adequate for comparisons within a study but are not accurate in terms of absolute intake, limiting the ability to compare cutpoints across studies (67). In general, the studies that found an association reported smoking-adjusted risk estimates for the highest category of alcohol examined, ranging from 1.6–2.2 for total alcohol, 1.4–3.4 for beer, 0.4–2.2 for wine, and 1.5–2.6 for hard liquor. Risk estimates of this magnitude are considered important in nutritional epidemiology, particularly considering the prevalence of the exposure (59, 67).

A significant dose-response relationship has been reported for total alcohol (11, 20, 24, 28, 29, 32), beer (20, 24), wine (33), and hard liquor (30). Nevertheless, some studies have suggested that the relationship with beer (22) or alcohol (11) may be U-shaped. In the ATBC study (33), drinkers of any type alcohol had lower risk of lung cancer than nondrinkers. Other studies have reported decreased lung cancer risk for light or occasional drinkers of total alcohol (11, 41, 28) or beer (13, 22, 24). If the reference category includes former drinkers, light or occasional drinking may appear to be associated with reduced risk because drinking lightly in the present may be better than drinking heavily in the past or being in poor health, if these were the reasons to quit drinking. It is also possible that drinking lightly is just part of a healthier life-style. Nonetheless, other studies did not find a protective effect for light drinkers (20, 29). In the Western New York Diet Study (20) only those drinking more than 40 drinks of beer per month had elevated lung cancer risk. A similar curve was seen in a prospective study conducted in Denmark (32), with increased risk for only those consuming more than 13 drinks per week of beer or hard liquor. If the relationship with beer or alcohol is not linear, as suggested by these investigators, some studies may have failed to find an association because they evaluated alcohol only as a continuous variable, or because the study population's intake may have fallen in the "flat" part of the curve.

Alternative explanation to the hypothesis should also be considered, in particular the confounding effects of smoking and dietary intake. If cigarette smoking is not carefully ascertained and controlled for, confounding by cigarette smoking would lead to an overestimation of risk estimates or to a spurious association. Studies have typically reported a substantial attenuation of risk estimates when cigarette smoking was included in the model. However, some degree of residual confounding by cigarette smoking may remain, in particular in studies that adjusted for smoking as a

categorical variable, with open-ended high smoking categories (9, 12, 24, 29, 31, 32, 41). Nonetheless, the relationship persisted in other studies after controlling for smoking history as a continuous variable (11, 20). Furthermore, Potter *et al.*, (22) stratified smoking history in pack-years in six categories and found an elevated Mantel-Haenszel OR for the highest tertile of beer drinking (OR: 1.9; 95% CI: 0.96–3.9). There was no evidence of residual confounding by smoking in this study because the mean cigarette use within smoking strata for cases and controls was very similar.

Diet is also an important factor to consider when evaluating the relationship between alcohol and lung cancer. Because of the caloric content of alcoholic beverages, their consumption may displace other elements of the diet, particularly for heavy drinkers. Also, the effects of ethanol on appetite, digestion, and absorption of nutrients is well documented (68). Diets high in fat and low in fruit consumption have been observed among heavy alcohol drinkers (69) and beer drinkers (70). Also, smokers tend to consume more high-fat foods (71) and less fruits and vegetables (72). In the Western New York Diet Study (20), however, the relationship between beer and lung cancer persisted after fat and carotenoid intakes were taken into account.

In conclusion, the current epidemiological evidence is suggestive of an increased lung cancer risk associated with drinking alcohol, particularly beer. The effect of alcohol by gender, race, smoking status, and histological type is not clear. The relationship between alcohol and lung cancer has been reported to be stronger or limited to subjects with low consumption of vegetables (24), vitamin A (9), or carotenoids (20). However, two chemoprevention trials (45, 47) reported that the increased lung cancer incidence among smokers associated with vitamin supplementation, including beta-carotene, was related to the amount of alcohol consumed. Ethanol has been shown in experimental studies to both promote a deficiency of vitamin A and exacerbate its toxicity as well as that of β -carotene (73), which may explain these contradictory findings.

Although the causal criteria are met to a certain degree within the framework of nutritional epidemiology, the overall evidence reviewed here is not deemed sufficient to consider alcohol to be causally related to lung cancer. However, we agree with the conclusion of the World Cancer Research Fund Expert Panel (3) that alcohol may be a "possible" cause of lung cancer, defined as "epidemiological studies are generally supportive, but are limited in quantity, quality or consistency." This conclusion warrants additional consideration of alcohol as a risk factor in lung cancer etiology, independent of cigarette smoking. Future studies need to conduct a detailed assessment of alcohol intake. Although the particular aspects of alcohol consumption that may increase risk are unknown, studies should, at a minimum, examine the separate effects of the different alcoholic beverages. Never drinkers should be clearly differentiated from former drinkers and the effect of past drinking should be evaluated. A detailed ascertainment and careful adjustment for smoking history is crucial. Studies should attempt to accrue sufficient lung cancer cases to properly examine the relationship with alcohol by sex, race, histological type, smoking status, and levels of intake of carotenoids and other dietary factors. Although it seems that the ideal study population may be never smokers, their low lung cancer incidence and alcohol consumption may limit the ability of the study to detect an association. Studies in populations where alcohol consumption is socially accepted, heterogeneous, and not highly correlated with cigarette smoking are likely to be the most informative. The nature of the relationship should be also evaluated and if the association is confirmed to be nonlinear, the classification of subjects into drinking categories should be based on

the curve's inflection point or on the threshold level so that a potential relationship is not missed.

Although cigarette smoking is undoubtedly the most important risk factor for lung cancer, the epidemiological evidence presented in this article warrants further investigation of the role of alcohol to improve our understanding of lung cancer etiology in nonsmokers and smokers.

Acknowledgments

We thank Dr. Lawrence H. Kushi for his invaluable advice during the revision of this manuscript.

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