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Association between alcohol and lung cancer in the alpha-tocopherol, beta-carotene cancer prevention study in Finland*

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Abstract

Objectives: We evaluated the association between alcohol intake and lung cancer in a trial-based cohort in Finland, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study).
Methods: During an average of 7.7 years of follow-up, 1059 lung cancer cases were diagnosed among the 27,111 male smokers with complete alcohol and dietary information. The relationship between alcohol and lung cancer was assessed in multivariate Cox regression models that adjusted for age, smoking, body mass index and intervention group.
Results: Nondrinkers, 11% of the study population, were at increased lung cancer risk compared to drinkers (RR = 1.2, 95% CI: 1.0–1.4), possibly due to the inclusion of ex-drinkers who had stopped drinking for health reasons. Among drinkers only, we observed no association between lung cancer and total ethanol or specific beverage (beer, wine, spirits) intake. We found no significant effect modification by level of smoking, dietary micronutrients or trial intervention group; however, for men in the highest quartile of alcohol intake, we observed a slight increase in risk for lighter smokers (<1 pack/day) and reduced risk among the heaviest smokers (>30 cigarettes/day).
Conclusions: We concluded that alcohol consumption was not a risk factor for lung cancer among male cigarette smokers, and its effect was not significantly modified by other factors, notably smoking history.

Introduction

Lung cancer remains the leading cause of cancer mortality in industrialized countries and throughout much of the world. While it is known that cigarette smoking is a major contributor to the occurrence of this usually fatal disease, it is less clear what other factors influence whether a smoker develops lung cancer: almost 90% of lung cancer is attributed to smoking, yet only 10% of smokers develop the disease. In light of this, greater insight is needed into the other nutritional, genetic and behavioral characteristics that modify the risk of a smoker developing lung cancer.

Alcohol consumption is an established risk factor for the tobacco-related cancers of the oral cavity, pharynx, esophagus, and larynx [1, 2]. Alcohol's role in cancer of the lung is less clear, however. Several epidemiological studies suggest a positive association between alcohol and lung cancer [2–8]. Many of the studies are inconclusive, however, in part because of inadequate adjustment for confounding by smoking and often poor assessment of alcohol intake. Confounding by total caloric intake and other dietary factors, particularly the several micronutrients that have been strongly related to lung cancer risk, are often not evaluated or considered. Alcohol could be etiologically related to lung cancer indirectly through the modulation of dietary patterns by heavy drinking [2, 9], through resulting nutrient deficiencies [10, 11], or through reduced plasma concentrations of vitamin A, carotenoids, folate, or other

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micronutrients [12, 13]. Possible direct effects on lung carcinogenesis include the induction of cytochrome P-450 enzymes that activate procarcinogens [14], increased production of free radicals due to the oxidation of ethanol into acetaldehyde (reviewed in [15]), or by impairment of DNA repair [16] and immune function [17, 18]. Moreover, alcohol appears to increase the risk associated with tobacco in head and neck cancers, indicating that there may be a synergistic effect between alcohol and carcinogens in tobacco smoke [19, 20].

We studied the independent role of alcohol consumption in lung carcinogenesis among participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. Where other observational studies of this hypothesis have been limited by small case numbers or inadequate smoking and dietary information, the ATBC Study cohort is large, and detailed diet and smoking histories were collected prospectively. Evaluation of the alcohol–lung cancer association was considered particularly relevant because of the Study's earlier findings suggesting that alcohol might potentiate the risk of lung cancer resulting from β-carotene supplementation [21].

Methods

Study population

The original study population consisted of 29,133 white male smokers participating in the Alpha-Tocopherol Beta-carotene Cancer Prevention (ATBC) Study conducted in Finland. The ATBC Study was a randomized, placebo-controlled trial designed to determine whether α-tocopherol (50 mg/day), β-carotene (20 mg/day), or both substances would reduce the incidence of lung and other cancers. The overall design, rationale and objectives of this study have been published [22]. Participants were recruited between 1985 and 1988 and followed during the active trial period until death or April 30, 1993 (median follow-up, 6.1 years). Cancer incidence was also ascertained post-intervention. Men who were aged 50 to 69 years, smoked five or more cigarettes per day and lived in southwestern Finland were eligible for inclusion in the study. Those excluded from the study were men who were alcoholics, who had cirrhosis of the liver, severe angina with exertion, chronic renal insufficiency, who had been previously diagnosed with cancer, or who were taking vitamins A, E, or β-carotene beyond certain dosages. The ATBC Study was approved by the institutional review boards of the National Cancer Institute (US) and the National Public Health Institute of Finland.

Data collection

Dietary, smoking and other background data, as well as height and weight and a serum sample were obtained at entry. The total amount and type of alcohol beverage consumed (*i.e.*, beer, wine and spirit) were estimated using a self-administered food-use questionnaire given to all participants prior to randomization. Of the entire cohort, 27,111 men (93.1%) completed the questionnaire. Using a color picture booklet as an aid, participants reported their usual frequency of consumption and portion sizes over the previous year for 276 common food items and beverages. This dietary instrument was measured for reproducibility and validity. The Pearson correlation coefficient of alcohol consumption was 0.9 for reproducibility and 0.8 for validity [24]. Dietary nutrient intake was estimated using food composition data available from the National Public Health Institute of Finland. Total alcohol intake was converted into grams of ethanol per day, while grams of intake of the specific alcoholic beverages were also calculated and assessed. Drinkers were defined as subjects who reported any alcohol intake, while nondrinkers were subjects who reported no alcohol intake.

Serum concentrations of β-carotene, α-tocopherol, and cholesterol were determined prior to the intervention analysis and the methods have been previously reported [21].

Case identification

Cases were defined as men who developed incident primary cancer of the lung or bronchus (ICD-9 = 162) diagnosed between May 1985 and December 1994. These cancers ($n = 1059$) were identified through the Finnish Cancer Registry and the Register of Causes of Death, which provided approximately 100% case ascertainment. Medical records were centrally reviewed by one or two study physicians who confirmed the diagnosis received from the Cancer Registry. Histological or cytological confirmation, using ICD-O classification, was made for 93% of the cases. Thirty-four percent of the cases were of squamous cell type, 18% were small cell type, 13% were adenocarcinomas, and 35% were of other cell types. Cases diagnosed during the trial intervention period ($n = 894$, or 84%) were additionally reviewed and staged by two study medical oncologists using the staging criteria of the American Joint Committee on Cancer [23]. The distribution of the cases by stage was 20%, 14%, 36%, and 30% for stages I, II, III, and IV, respectively.

Statistical analyses

All statistical analyses were performed using the Statistical Analysis Systems (SAS) software package [25, 26]. Cox regression methods [27], using follow-up time as the underlying time metric, were performed to estimate the relative risk and 95% confidence intervals of incident lung cancer associated with alcohol consumption. We evaluated the association between alcohol and incident lung cancer through three predictor variables of alcohol: ethanol modeled as a continuous variable; a categorical indicator (1,0) representing drinkers *vs.* nondrinkers; and categorical indicators for the quartiles of alcohol intake among drinkers, using the first quartile as reference, and keeping nondrinkers as a separate category. Both total ethanol intake and consumption of specific alcoholic beverages were analyzed.

Means and standard deviations of study factors for the alcohol categories were derived using age as a continuous variable in linear regression models. Although alcohol and total energy intake were not highly correlated ($r = 0.15$) because ethanol is a source of calories, we evaluated whether energy-adjustment of alcohol was necessary by modeling it as, (1) unadjusted, (2) (natural) log-transformed alcohol adjusted for total energy intake according to the residual method described by Willett [28], and (3) by including total energy intake as a continuous covariate factor in the hazards model. Models from the three approaches yielded similar risk estimates for alcohol. Vitamin supplement use of folate, vitamin C, vitamin A, and vitamin E was evaluated by adding supplementation sources to dietary intake to provide total vitamin intake. Multivariable models were developed by including the variable of interest, alcohol, into a base model for lung cancer previously described [21]. This model included baseline age, number of cigarettes smoked daily, years of cigarette smoking, and body mass index (BMI, calculated as weight (kg) divided by height $(m)^2$) as continuous variables, along with α-tocopherol and β-carotene intervention group assignment. α-Tocopherol and β-carotene supplementation were evaluated by inclusion of its indicator term into the model, and effect modification by intervention assignment (α-tocopherol, β-carotene, or both) was evaluated as described below. The p values for trends among drinkers were based on the statistical significance of the coefficients of the various alcohol variables as quartiles scored 1 through 4. Effect modification of study factors was tested by inclusion of that factor and its cross-product term with alcohol in the hazards models, and through subgroup analysis using stratification according to median split or tertile categories of factors. The validity of the proportional hazard assumption was tested by including in our model a cross-product term between the log of follow-up time and alcohol modeled as a continuous and as a single categorical (any/none) variable.

Results

There were 1059 men diagnosed with incident lung cancer in the cohort of 27,111. Median follow-up time was 7.7 years, and a total of 196,064 person-years of observation accumulated. Eighty-nine percent consumed alcohol in some form, with consumption ranging from 0 to 278 grams of ethanol per day. Most alcohol consumers drank spirits (81%), followed by beer (71%), and then wine (21%). On average, the participants smoked a pack of cigarettes daily and had smoked for 36 years at baseline. Nineteen percent of the participants quit smoking for at least two consecutive study visits (*i.e.*, for at least 8 months), with 58% of these quitting during the first three years of follow-up, and 42% quitting later in the study. There was no difference in the smoking cessation rate observed between drinkers and nondrinkers ($\chi^2 = 0.76$).

Age-adjusted mean demographic characteristics, dietary intakes, and smoking history at baseline of the subjects according to level of alcohol consumption are shown in Table 1. Average age, serum β-carotene concentration, and dietary vitamin C and β-carotene generally decreased with increasing alcohol consumption. In contrast, the number of cigarettes smoked per day, and total energy consumed rose with increasing alcohol consumption. The other factors were not appreciably related to alcohol.

We first assessed the association between lung cancer and alcohol as drinking status (any/none) and found that, except for consumers of spirits, drinkers were at decreased risk compared to nondrinkers for all beverage types. The relative risks (RR) and 95% confidence intervals (CI) were: for total ethanol, RR = 0.8 (CI, 0.7–1.0); spirits, RR = 0.9 (CI, 0.8–1.1); beer, RR = 0.9 (CI, 0.8–1.0); and wine, RR = 0.8 (CI, 0.7–1.0). This finding is consistent with several studies reporting U-shaped risk associations for alcohol, with low level and moderate drinkers having the lowest cancer risk [3–6, 29]. Therefore, in the subsequent analysis, we kept nondrinkers as a separate category, and used the lowest quartile of drinkers as the referent category.

Table 2 shows the adjusted RRs and corresponding 95% CIs for lung cancer by level of alcohol consumption measured as total ethanol and as the beverage subtypes. In all models, adjustment was made for age at randomization, BMI, cigarettes smoked per day, total

Table 1. Selected age-adjusted[a] baseline characteristics by level of alcohol consumption, Finnish men

Factor Range (median (g/day))	Alcohol consumption categories[b] (ethanol, g/day)				
	Non-drinkers	0.04–5.2 (1.8)	5.3–13.3 (8.7)	13.4–27.6 (20.6)	27.7–278.5 (42.0)
Number of Subjects	3034	5687	6198	6000	6012
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	58.4 (5.3)	58.1 (5.2)	57.3 (5.0)	56.7 (4.8)	56.0 (4.7)
Years smoked	36.3 (7.0)	35.1 (7.4)	35.6 (7.1)	36.1 (6.8)	36.6 (6.5)
Cigarettes/day	19.9 (8.7)	18.7 (8.0)	19.7 (8.2)	20.7 (8.3)	22.9 (9.4)
BMI (kg/m^2)	26.1 (3.9)	26.0 (3.6)	26.4 (3.7)	26.4 (3.8)	26.5 (3.9)
Serum cholesterol (mmol/L)	6.3 (1.3)	6.2 (1.1)	6.3 (1.2)	6.2 (1.2)	6.2 (1.1)
Serum α-tocopherol (mg/L)	11.9 (2.6)	12.0 (2.4)	12.0 (3.0)	12.0 (2.8)	11.7 (3.2)
Serum β-carotene (μg/L)	272 (224)	253 (193)	224 (189)	191 (152)	156 (165)
Dietary intake (daily)					
Energy (kcal)	2777 (818)	2758 (751)	2749 (760)	2802 (760)	2970 (811)
Fat (g)	125.1 (43.4)	122.9 (39.4)	123.0 (40.2)	122.8 (40.0)	121.6 (42.2)
Vitamin A (μg)	2079 (1468)	2227 (1469)	2218 (1579)	2225 (1566)	2226 (1607)
Betacarotene (μg)	2199 (1740)	2261 (1594)	2164 (1583)	2104 (1476)	1981 (1402)
Vitamin C (mg)	95.4 (46.3)	100.4 (45.9)	97.3 (44.4)	96.0 (45.0)	91.1 (45.0)
Vitamin E (mg)	12.1 (5.8)	12.2 (5.6)	12.1 (5.7)	12.1 (5.6)	11.8 (5.9)
Folate (μg)	337 (106)	342 (100)	335 (101)	335 (102)	337 (106)

[a] Means and standard deviations were age-adjusted using age as a continuous variable in linear regression models.
[b] Alcohol categorized as nondrinkers and by quartile of ethanol intake among drinkers.

years smoked, and β-carotene intervention group. Among men who drank, we saw no overall effect on lung cancer risk for level of alcohol intake. The RR estimates were unchanged by further adjustment for dietary intake of energy (kcal), folate, fat, cholesterol, dietary β-carotene, carotenoids, vitamin A, vitamin C, or vitamin E, or the other alcohol subtypes.

The observed risk increase among nondrinkers compared to drinkers led us to consider whether abstaining may have been the result of failing health, and not the

Table 2. Adjusted relative risks (RR)[a] and 95% confidence intervals (CI) of lung cancer by level of consumption of alcohol subtypes, Finnish men

Subtype	Category (range/(median))	Cases	Person yr	RR	95% CI	*p* trend
Alcohol (g/day)	non-drinkers	154	21466	1.2	(0.9–1.4)	0.89
(total ethanol)	Q1[b] 0.04–5.2/(1.8)	233	42464	1.0		
	Q2 5.3–13.3/(8.7)	234	44874	1.0	(0.8–1.2)	
	Q3 13.4–27.6/(20.6)	208	43725	0.9	(0.8–1.1)	
	Q4 27.7–278.5/(42.0)	230	43535	1.0	(0.8–1.2)	
Spirits (g/day)	non-drinkers	232	36303	1.1	(0.9–1.3)	0.12
	Q1 0.01–2.6/(0.9)	210	41043	1.0		
	Q2 2.7–10.6/(5.3)	221	41687	1.0	(0.9–1.3)	
	Q3 10.7–22.7/(10.7)	204	39433	1.1	(0.9–1.3)	
	Q4 22.8–160.0/(22.9)	192	37416	1.1	(0.9–1.3)	
Beer (g/day)	non-drinkers	363	56769	1.0	(0.9–1.2)	0.19
	Q1 0.01–1.6/(0.9)	192	35126	1.0		
	Q2 1.7–4.5/(3.0)	157	35743	0.8	(0.6–1.0)	
	Q3 4.6–11.5/(6.6)	154	33599	0.9	(0.7–1.1)	
	Q4 11.6–242.6/(19.8)	193	34829	0.9	(0.7–1.1)	
Wine (g/day)	non-drinkers	878	153622	1.1	(0.9, 1.3)	0.02
	Low 0.09–2/(0.7)	98	21050	1.0		
	High 2.1–67.5/(4.6)	83	21392	0.8	(0.6–1.1)	

[a] RR after adjusting for age, body mass index, years smoked, cigarettes per day, and intervention group.
[b] Alcohol categorized as nondrinkers and by quartile of ethanol intake among drinkers.
[c] *p* for trend is for Q1–Q4 only.

cause of lung cancer. To address this, we compared hazards computed using nondrinkers as the referent with the first three years of follow-up excluded, and found the risk estimates were not altered. In addition, evaluation of the proportional hazards assumption revealed that the hazards for drinking status did not change over time.

Since previous studies indicated that alcohol may be most harmful for squamous cell carcinomas [8, 30], we evaluated the relationship between alcohol and lung cancer by histological type. We observed a modest positive association for adenocarcinoma and no association for small or squamous cell carcinoma. Men in the highest compared to the lowest quartile of intake had an adjusted RR of 1.7 (CI, 1.0–2.8) for adenocarcinoma, 1.2 (CI, 0.8–1.9) for small cell lung cancer, 0.8 (CI, 0.6–1.1) for squamous cell carcinoma, and 1.1 (CI, 0.6–1.7) for all other lung cancer histological subtypes combined (data not shown). Although we observed an association for adenocarcinoma, there was no dose response relationship. None of the tests for trend were significant, however (p for trend was 0.22, 0.87, 0.15, and 0.98 for adenocarcinoma, small cell, squamous cell, and all other types, respectively).

The results from hazards models conducted within categories of cigarette smoking exposures, including daily cigarettes smoked, years of smoking, inhalation, and cessation of smoking are shown in Table 3. We found little evidence of an interaction between alcohol and level of cigarette smoking in this cohort of smokers. Among men smoking less than 20 cigarettes daily, however, a modest though non-significant increase in the highest compared to the lowest quartile of alcohol intake was observed. In contrast, a slight though non-significant inverse association between alcohol consumption and lung cancer was observed in the heaviest smokers (>30 cigarettes/day). Age-standardized lung cancer incidence rates according to levels of alcohol intake and cigarette smoking are shown in Figure 1. Incidence showed a suggestion of a U-shaped relationship to alcohol among all smoking categories. The figure highlights the fact that the highest rates are among nondrinkers and very light drinkers regardless of smoking category, although the effect is most striking among heavy smokers.

Several other factors were evaluated for effect modification of the alcohol association, including dietary intake of energy, vitamin C, vitamin E, folate, fat, serum nutrients (β-carotene, α-tocopherol, and retinol), age, BMI, education, and physical activity, and no significant interactions were found (data not shown). For example, the RR and 95% CI for the highest versus the lowest

Table 3. Adjusted relative risks[a] (RR) and 95% confidence intervals (CI) of lung cancer associated with alcohol consumption according to cigarette smoking exposures and allocation of intervention assignment, Finnish men

	Categories of alcohol consumption[b] (g/day)					
	non-drinkers	0–5.2	5.3–13.3	13.4–27.6	27.7+	p trend[c]
	RR (95% CI)	RR	RR (95% CI)	RR (95% CI)	RR (95% CI)	
Cigarettes/day						
<20	1.2 (0.8–1.7)	1.0	0.9 (0.7–1.3)	0.9 (0.6–1.3)	1.2 (0.8–1.7)	0.59
20–29	1.2 (0.9–1.6)	1.0	1.1 (0.8–1.4)	1.0 (0.7–1.3)	1.0 (0.8–1.4)	0.99
+30	1.0 (0.6–1.6)	1.0	0.9 (0.6–1.3)	0.8 (0.5–1.2)	0.8 (0.5–1.2)	0.26
Years smoked						
<32	1.4 (0.7–2.9)	1.0	1.1 (0.6–2.1)	1.1 (0.6–2.1)	1.0 (0.5–1.9)	0.87
32–40	1.4 (1.0–2.0)	1.0	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.3 (0.9–1.7)	0.16
>40	1.0 (0.8–1.3)	1.0	0.9 (0.7–1.2)	0.8 (0.6–1.0)	0.9 (0.7–1.1)	0.13
Inhale						
Seldom	1.4 (0.7–2.8)	1.0	0.8 (0.4–1.7)	0.7 (0.3–1.5)	0.7 (0.3–1.7)	0.37
Often	1.4 (1.0–2.0)	1.0	1.2 (0.9–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	0.81
Always	1.0 (1.0–1.3)	1.0	0.9 (0.7–1.1)	0.8 (0.7–1.1)	1.0 (0.8–1.2)	0.84
Cessation[d]						
<3 yrs	1.2 (0.7–2.0)	1.0	0.8 (0.5–1.4)	1.1 (0.6–2.0)	0.9 (0.5–1.8)	0.67
>3 yrs	1.2 (0.6–2.6)	1.0	0.9 (0.4–1.8)	0.8 (0.4–1.7)	1.5 (0.7–3.2)	0.81
Never	1.2 (0.9–1.5)	1.0	1.0 (0.8–1.2)	0.9 (0.7–1.1)	1.0 (0.8–1.2)	0.16

[a] RR after adjusting for age, body mass index, years smoked, cigarettes per day, and treatment group.
[b] Alcohol categorized as nondrinkers and by quartile of ethanol intake among drinkers.
[c] p for trend is for Q1–Q4 only.
[d] Cessation is defined as having quit smoking for at least 2 consecutive follow-up visits (8 months) either early during follow-up (<3 years) or late during follow-up (<3 years), or never having quit.

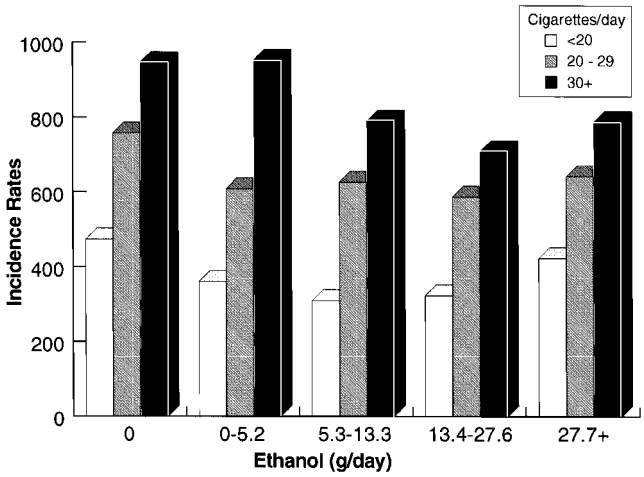

Fig. 1. Age-adjusted lung cancer incidence per 100,000 years according to level of alcohol and cigarette use.

quartile of alcohol intake among drinkers was 1.0 (CI, 0.8–1.4) and 1.0 (CI, 0.8–1.2) for younger ($\leq$57 years) versus older (>57 years) men, 1.0 (CI, 0.8–1.2) and 1.0 (CI, 0.8–1.4) for those with dietary folate intake of $\leq$325 μg/day versus >325 μg/day, and 0.9 (CI, 0.7–1.2) and 1.0 (CI, 0.7–1.4) for those with serum β-carotene $\leq$175 μg/L versus >175 μg/L (p for interaction with alcohol was 0.63, 0.39, and 0.58 for age, folate, and serum β-carotene, respectively).

Discussion

We found no evidence to support a positive association between lung cancer and either total alcohol intake or beer, wine or spirits consumption in smokers, after adjustment for several important potential confounders including age, cigarettes per day, years of smoking, body mass index, and β-carotene intervention. In fact, nondrinkers were at increased risk compared to drinkers, a finding that held true for each beverage type. An interaction between alcohol and level of cigarette smoking was suggested but not statistically significant, and there was no indication of effect modification by age, BMI, dietary factors, or by either of the trial interventions (*i.e.*, β-carotene or α-tocopherol supplementation). (We had previously reported a marginally significant positive interaction for lung cancer between alcohol and β-carotene supplementation in this study [21]: p for trend was 0.08 for alcohol modeled as scored quartiles and 0.05 for alcohol as a continuous variable; however, the present analysis includes almost two post-intervention years of observation and nearly 200 additional cases). The alcohol association did not differ materially by lung cancer histological type.

Of the previous cohort studies which adequately controlled for smoking, some [3, 7] but not all [30, 31] showed a positive association between alcohol consumption and lung cancer. A case-control study of Turkish men found a stronger association when alcohol was quantified as years of drinking rather than as amount [8]. Other case-control studies have reported isolated increased risk for specifc beverage subtypes, with beer being the most consistently related [4, 32]. Compared with most of these previous reports, the present investigation obtained more detailed alcohol exposure, including portion size and frequency of consumption for several beverage subtypes, with specific corresponding ethanol content (such as for light, medium, and strong beer). Our estimate of alcohol exposure was based on usual frequency and quantities of consumption over the past year prior to study entry, however, and did not query binge drinking or lifetime duration of alcohol use, which may be important alternative predictors of risk.

An explanation for both our findings of increased risk among nondrinkers and no association by level of alcohol among drinkers may be misclassification of alcohol exposure; that is, ex-drinkers may have been classified as nondrinkers and heavy drinkers may have under-reported consumption for the year before entering the study. Although the validity of self-reported alcohol consumption is generally considered to be good [33], and we obtained a correlation coefficient of 0.8 between alcohol from diet records and the questionnaire used here [24], underestimation of consumption by heavy drinkers has been previously documented [34]. Further, a study of alcohol and mortality in British men revealed that men tend to reduce their alcohol intake as they get older, with the heaviest drinkers making the biggest reductions [35]. In this study the nondrinkers were on average, older, smoked less per day, and consumed fewer calories and micronutrients such as vitamin C and vitamin A.

We observed the highest lung cancer rates among the nondrinkers suggesting that these subjects may have stopped or reduced drinking due to failing health. Prior studies which have considered ex-drinkers and never drinkers separately found that ex-drinkers have the highest mortality, even higher than heavy drinkers [7, 29]. Since information regarding changes in drinking patterns was not obtained, we sought to explore misclassification of ex-drinkers as nondrinkers by evaluating changes in lung cancer risk among drinkers compared to nondrinkers over time. Although we previously reported that abstinence appeared harmful early in follow-up for colorectal cancer [36], this was not true for lung cancer. Another possible explanation for

increased risks in nondrinkers is that consumption of small quantities of alcohol is necessary for induction of several protective enzymes, such as alcohol metabolizing enzymes, DNA repair enzymes, and carcinogen detoxification enzymes.

The ATBC Study included only current smokers of at least five cigarettes daily. Our results effectively rule out a strong harmful effect of ethanol in smokers, and make it more likely that smoking confounded the alcohol associations in previous studies in which smoking was less controlled. On the other hand, the men may have been at such elevated risk for developing lung cancer that any incremental risk incurred from alcohol consumption was negligible. We did observe slightly increased risk with higher alcohol intake among lighter smokers, while among heavy smokers, a risk reduction was suggested. There is some experimental evidence in support of alcohol having a detrimental effect in light smokers or nonsmokers only; for example, by alcohol variably potentiating carcinogens depending upon the amount of carcinogen present [37, 38]. Alcohol is considered to act as a competitive inhibitor for cytochrome p450-2E1 in the liver, rendering the liver unable to detoxify all of the 2E1-associated carcinogens derived from smoking and resulting in higher concentrations in post-hepatic sites such as the lung. Studies conducted in mice show that co-treatment with alcohol and the potent carcinogen *N*-nitrosodimethylamine (NMDA) result in a 40-fold increase in NDMA levels in the blood and lung, compared to the administration of NDMA alone [37]. This was only observed for modest levels of the NDMA administration, however, whereas at high exposure, NDMA levels in the blood and lung were high, regardless of alcohol co-administration.

The inverse relationship suggested for the heavier smokers may be explained by a healthy participant effect, since entry into the ATBC Study required that there was no evidence of a serious chronic disease or alcoholism. Therefore, it is possible that the men who were both heavy smokers and heavy drinkers and would have been at high risk but had already developed alcohol-related diseases were excluded from the study. Other studies have also found evidence for effect modification of alcohol by tobacco smoke. For example, Stocks *et al.* [39], observed increased lung cancer risk associated with frequent beer drinking only among nonsmokers and light smokers (<100 cigarettes/week), and Murata *et al.* [5] found that alcohol had an impact in nonsmokers only. In contrast, in the case-control study of Bandera *et al.* [4] and the New York State Cohort alcohol and diet study [30], associations between alcohol and lung cancer were limited to heavier smokers.

In conclusion, we observed no association between alcohol and lung cancer in this population of cigarette smokers, although nondrinkers appeared to be at somewhat increased risk compared to drinkers. It is possible that alcohol plays a greater etiologic role in lung cancer development in nonsmokers or light smokers who have smaller cumulative carcinogenic exposures as compared with heavier smokers. Additional observational studies are needed to explore this hypothesis and possibly to further evaluate the relationship between alcohol and lung cancer in heavy smokers using alternative measures of alcohol consumption such as lifetime drinking patterns and histories (including assessment of binge drinking). Given the high prevalence of alcohol consumption and lung cancer both in the US and worldwide, the knowledge gained from such additional work could have substantial public health impact.

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References

1. Leo MA, Lieber CS (1985) New pathway for retinol metabolism in liver microsomes. *J Biol Chem* **260**: 5228–5231.
2. Adami H-O, McLaughlin JK, Hsing AW, *et al.* (1992) Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control* **3**: 419–425.
3. Potter JD, Sellers TA, Folsom AR (1992) Alcohol, beer and lung cancer in postmenopausal women. The Iowa Women's Health Study. *Ann Epidemiol* **2**: 587–595.
4. Bandera EV, Freudenheim JL, Graham S, *et al.* (1992) Alcohol consumption and lung cancer in white males. *Cancer Causes Control* **3**: 361–369.
5. Murata M, Takayama K, Choi BC, Pak AW (1996) A nested case-control study on alcohol drinking, tobacco smoking, and cancer. *Cancer Detect Prev* **20**: 557–565.
6. Pollack ES, Nomura AMY, Heilbrun LK, Stemmermann GN, Green SB (1984) Prospective study of alcohol consumption and cancer. *N Eng J Med* **310**: 617–621.
7. Kono S, Ikeda M, Tokudome S, Nishizumi M, Kuratsune M (1986) Alcohol and mortality: a cohort study of male Japanese physicians. *Int J Epidemiol* **15**: 527–532.
8. Dosemeci M, Gokmen I, Unsal M, Hayes R, Blair A (1997) Tobacco, alcohol use, and risks of laryngeal and lung cancer by subsite and histologic type in Turkey. *Cancer Causes Control* **8**: 729–737.
9. Hillers V, Massey L (1985) Interrelationships of moderate and high alcohol consumption with diet and health status. *Am J Clin Nutr* **41**: 356–362.

10. Lieber CS, Garro A, Leo M, Mak K, Worner T (1986) Alcohol and cancer. *Hepatology* **6**: 1005–1019.
11. Morgan MY (1982) Alcohol and nutrition. *Br Med Bull* **38**: 21–29.
12. Forman M, Beecher G, Lanza E, *et al.* (1995) Effect of alcohol consumption on plasma carotenoid concentrations in premenopausal women: a controlled dietary study. *Am J Clin Nutr* **62**: 131–135.
13. Rimm E, Colditz G (1993) Smoking, alcohol, and plasma level of carotenes and vitamin E. *Ann N Y Acad Sci* **686**: 323–334.
14. Lieber CS (1997) Cytochrome P-4502E1: its physiological and pathological role. *Physiol Rev* **77**: 517–544.
15. Brooks PJ (1977) DNA damage, DNA repair, and alcohol toxicity – a review. *Alcohol Clin Exp Res* **21**: 1073–1082.
16. Topinka J, Binkova B, Sram R, Fojtikova I (1991) DNA-repair capacity and lipid peroxidation in chronic alcoholics. *Mutat Res* **263**: 133–136.
17. Mufti SI, Prabhala R, Moriguchi S, *et al.* (1988) Functional and numerical alterations induced by ethanol in the cellular immune system. *Immunopharmacology* **15**: 85–94.
18. Waston R, Borgs P, Witte M, *et al.* (1994) Alcohol, immunomodulation, and disease. *Alcohol Alcohol* **29**: 131–139.
19. Kato I, Nomura AMY, Stemmermann GN, Chyou P-H (1992) Prospective study of the association of alcohol with cancer of the upper aerodigestive tract and other sites. *Cancer Causes Control* **3**: 145–151.
20. Blot W, McLaughlin J, Winn D, *et al.* (1998) Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res* **48**: 3282–3287.
21. Albanes D, Heinonen OP, Taylor PR, *et al.* (1996) α-Tocopherol and β-carotene supplements and lung cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: effects of base-line characteristics and study compliance. *J Natl Cancer Inst* **88**: 1560–1570.
22. ATBC Cancer Prevention Study Group (1994) The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics, and compliance. *Ann Epidemiol* **4**: 1–10.
23. American Joint Committee on Cancer (AJCC) (1992) Lung. In: Beahrs OH, Hensen DE, Hutter RV, Myers MH, eds. *Manual for Staging of Cancer, 4th ed.* Philadelphia: Lippincott, pp. 115–122.
24. Pietinen P, Hartman AM, Haapa E, *et al.* (1988) Reproducibility and validity of dietary assessment instruments. *Am J Epidemiol* **128**: 655–666.
25. SAS Institute, Inc. (1996) SAS/STAT Software Changes and Enhancements through Release 6.11: The PHREG Procedure. Cary, NC: SAS Institute.
26. SAS Institute, Inc. (1994) SAS/STAT User's Guide, Version 6, 4th ed. Cary, NC: SAS Institute Inc.
27. Cox D (1972) Regression models and life-tables. *J R Soc B* **34**: 187–220.
28. Willett W (1990) Implications of total energy intake for epidemiologic analyses. In: Willett W, ed. *Nutr Epidemiol.* Oxford University Press.
29. Klatsky A, Friedman G, Siegelaub A (1981) Alcohol and mortality. *Ann Intern Med* **95**: 139–145.
30. Bandera E, Freudenheim J, Marshall J, *et al.* (1997) Diet and alcohol consumption and lung cancer risk in the New York State Cohort. *Cancer Causes Control* **8**: 828–840.
31. Gordon T, Kannel W (1984) Drinking and mortality: The Framingham Study. *Am J Epidemiol* **120**: 97–107.
32. Stefani ED, Correa P, Fierro L, Fontham ET-H, Chen V, Zavala D (1993) The effect of alcohol on the risk of lung cancer in Uruguay. *Cancer Epidemiol Biomarkers Prev* **2**: 21–26.
33. Giovannucci E, Colditz G, Stampfer M, *et al.* (1991) The assessment of alcohol consumption by a simple self-administered questionnaire. *Am J Epidemiol* **133**: 810–817.
34. Poikolainen K (1985) Underestimation of recalled alcohol intake in relation to actual consumption. *Br J Addiction* **80**: 215–216.
35. Shaper A, Wannamethee G, Walker M (1988) Alcohol and mortality in British men: explaining the U-shaped curve. *Lancet* 1267–1273.
36. Glynn S, Albanes D, Pietinen P, *et al.* (1996) Alcohol consumption and risk of colorectal cancer in a cohort of Finnish men. *Cancer Causes Control* **7**: 214–223.
37. Anderson L, Koseniauskas R, Burak E, *et al.* (1994) Suppression of *in vivo* clearance of N-nitrosodimethylamine in mice by cotreatment with ethanol. *Drug Metab Dispos* **22**: 43–49.
38. Anderson L, Souliotis V, Chhabra S, Moskal T, Harbaugh S, Krytopoulos S (1996) N-nitrosodimethylamine-derived O6-methylguanine in DNA of monkey gastrointestinal and urogenital organs and enhancement by ethanol. *Int J Cancer* **66**: 130–134.
39. Stocks P (1975) Cancer incidence in north Wales and Liverpool region in relation to habits and environment. *British Empire Cancer Campaign 35th Annual Report*, Part II (Suppl). London: Her Majesty's Stationery Office.