Alcoholic Beverage Intake and Risk of Lung Cancer: The California Men's Health Study

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Abstract

We investigated the effect of alcoholic beverage consumption on the risk of lung cancer using the California Men's Health Study.

Methods: **The California Men's Health Study is a multiethnic cohort of 84,170 men ages 45 to 69 years who are members of the Kaiser Permanente California health plans. Demographics and detailed lifestyle characteristics were collected from surveys mailed between 2000 and 2003. Incident lung cancer cases were identified by health plan cancer registries through December 2006 (n = 210). Multivariable Cox's regression was used to examine the effects of beer, red wine, white wine (including rosé), and liquor consumption on risk of lung cancer adjusting for age, race/ethnicity, education, income, body mass index, history of chronic obstructive pulmonary disease/emphysema, and smoking history.**

Results: **There was a significant linear decrease in risk of lung cancer associated with consumption of red wine among ever-smokers: hazard ratio (HR), 0.98; 95% confidence interval (95% CI), 0.96-1.00 for increase of 1 drink per month. This relationship was slightly stronger among heavy smokers (≥20 pack-years): HR, 0.96; 95% CI, 0.93-1.00. When alcoholic beverage consumption was examined by frequency of intake, consumption of ≥1 drink of red wine per day was associated with an approximately 60% reduced lung cancer risk in ever-smokers: HR, 0.39; 95% CI, 0.14-1.08. No clear associations with lung cancer were seen for intake of white wine, beer, or liquor.**

Conclusion: **Moderate red wine consumption was inversely associated with lung cancer risk after adjusting for confounders. Our results should not be extrapolated to heavy alcohol consumption.** (Cancer Epidemiol Biomarkers Prev 2008;17(10):2692–9)

Introduction

Lung cancer is the leading cause of cancer death in both men and women in the United States (1). Approximately 213,380 new cases and 160,390 lung cancer deaths were expected to occur in 2007 (1). A possible link between alcohol consumption and risk of lung cancer has long been speculated (2). However, epidemiologic studies have not provided consistent evidence on the effect of alcohol drinking on lung cancer. Several studies have suggested that different types of alcoholic beverages may have different effects on risk of lung cancer (3-5). Furthermore, major gaps in the literature limit our ability to understand the nature of the associations observed. For example, many previous studies only adjusted for pack-years of smoking, which is known to serve as an imperfect control for the effect of tobacco smoking. Few studies adjusted for other lung cancer-related factors such as passive smoking, socioeconomic status, and dietary intake, although all of these are known to be strongly associated with use of alcoholic beverages (6-9).

To address these issues, we conducted a prospective cohort study controlling for known and potentially important confounders using the detailed smoking history and lifestyle data collected in the California Men's Health Study (CMHS). We also examined the association by type of alcoholic beverage among smokers and lung cancer histology.

Materials and Methods

Study Cohort. CMHS is a multiethnic cohort of men who are members of the northern and southern California regions of Kaiser Permanente, the largest managed care organization in California. Eligible participants included all male Kaiser Permanente California members, ages 45 to 69 years in January 2000, who had been members of the health plan for at least 1 year at recruitment. Nearly 850,000 men met the eligibility criteria. Recruitment was carried out between January 2002 and December 2003 using a two-step process in three waves of mailing. A total of 84,170 men including a nearly 40% minority participation completed the questionnaires and hence joined the cohort. Details of the cohort design and recruitment methods were described previously by Enger et al (10). The CMHS cohort was similar to the population of health plan members on important characteristics and appeared similar to men who responded to a general health survey in California (California Health Interview Survey) on a variety of important demographic and clinical characteristics (10). Between study baseline and December 2006, 11,144 men in the cohort terminated their health plan membership, resulting in a follow-up rate of 87% by end of the 2006.

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Questionnaire. The questionnaires collected information on demographics, country of origin, income, anthropometrics, family history of cancer, existing health conditions, medication/drug use, physical activity, and tobacco smoking. Information on alcohol, dietary, and multivitamin intake was elicited with a detailed semiquantitative food frequency questionnaire adapted from the Women's Health Initiative and other studies and modified for men's health (11-14). Frequency of consumption of beer, red wine, white or rosé wine, and liquor was assessed by the following categories: 0 or <1 drink/mo, 1 to 3 drinks/mo, 1 drink/wk, 2 to 4 drinks/wk, 5 to 6 drinks/wk, 1 drink/d, 2 to 3 drinks/d, 4 to 5 drinks/d, or ≥6 drinks/d. The size of the drink relative to the standard serving size (12 ounce can or bottle for beer, 6 ounce glass for wine, and 1.5 ounce shot for liquor) was also elicited. Total alcohol consumption was derived by summing the consumption of each alcoholic beverage type.

Tobacco smoking status was ascertained with the question, ''Have you smoked at least 100 cigarettes in your lifetime?'' For those who answered ''yes'' (ever-smokers), the questionnaire also asked the total number of years smoked and average number of cigarettes smoked per day. For former smokers, duration of quitting was elicited. The questionnaire also collected information on exposure to secondhand smoke in childhood and adulthood at home, in the work place, and in bars/restaurants or other nonhome locations.

Ascertainment of Lung Cancer. Incident lung cancer in this cohort was identified from the health plans' cancer registries. The registries contain data on all patients who were diagnosed and/or treated for a new cancer since 1988. Cancer case ascertainment is expected to be highly valid (with an estimated sensitivity of ≥99%), as reporting of cancers is mandated under state law and cancer patient abstracts are sent to the State of California Cancer Registry and the National Cancer Institute Surveillance, Epidemiology, and End Results program. To identify incident cases, we performed computer matches on the unique Kaiser Permanente medical record number of registry lung cancer cases between 2002 and 2006 and the entire CMHS cohort. The registries provided data on date of diagnosis and lung cancer histologic type. A total of 269 incident lung cancer among the CMHS members were identified between study baseline (2002-2003) and December 2006.

Exclusion Criteria. Men who reported having had any previous cancer diagnosis (except nonmelanoma skin cancer) were excluded from the analyses (n = 5,976). Lung cancer cases diagnosed within 6 months after study baseline (28 cases) were also excluded to avoid temporal ambiguity of alcohol use and other reported behaviors. After the exclusion, 78,168 men (210 lung cancer cases) were left in the analytical dataset.

Statistical Analysis. We first calculated the distribution of demographic characteristics, alcoholic beverage consumption, smoking history, and dietary intake for lung cancer cases and noncases. Crude associations between these variables and lung cancer status were obtained using χ^2 tests for categorical variables and logistic regression for continuous variables. To understand the associations between consumption of different types of alcoholic beverages and health-related lifestyle factors, distributions of demographics, tobacco smoking, and dietary intake were calculated across levels of intake for each type of alcoholic beverage. The χ^2 test was used to test the association between different levels of consumption of each type of alcoholic beverage and these health-related lifestyle factors.

Multivariable Cox's regression was used to investigate the association between alcoholic beverage consumption and time to lung cancer. Follow-up started at the time of the baseline survey and ended at the time of lung cancer diagnosis, diagnosis of other cancers, termination of health plan membership, death or end of year 2006, which ever came first. Race/ethnicity, education, household income, body mass index (BMI; <18.5, 18.5-24.9, 25-29.9, ≥30 kg/m^2), history of chronic obstructive pulmonary disease (COPD)/emphysema, and tobacco smoking were adjusted for in the regression models, whereas age was used as the time axis in the survival analysis. The consumption of different types of alcoholic beverages was mutually adjusted for in the model. Each type of alcoholic beverage was modeled by three frequency categories: <1 drink/wk, ≥1 drink/wk but <1 drink/d and >1 drink/d, in reference to nondrinkers. The ''nondrinkers'' group was defined specific to each type of alcoholic beverage. The nondrinkers could include those who drank that type of alcoholic beverage occasionally (<1 drink/mo). Alcoholic beverage consumption was also modeled as a continuous variable in the unit of number of drinks per month. The continuous variable was converted from the categorical drinking variables by taking the midpoint of the consumption range. The category of ''≥6 drinks/d'' was converted into 180 drinks/mo. The effect of combined alcohol consumption was also examined when there was no obvious heterogeneity in the effects of different types of alcoholic beverages on the risk of lung cancer. The effect of combined alcohol consumption was modeled by four frequency categories: <1 drink/d, ≥1 but <2 drinks/d, ≥2 but <3 drinks/d, and ≥3 drinks/d in reference to nondrinkers.

To better control for the effect of tobacco smoking, we compared a model that contained pack-years versus one with separate variables for smoking duration and daily intensity. The latter model resulted in a smaller value of Akaike's Information Criterion. Therefore, we modeled smoking by including smoking status (never, current and quit ≤5 years, quit for 6-9 years, and quit for ≥10 years), duration of smoking (≤10, 11-20, 21-30, 31-40, and ≥41 years), and average number of cigarettes smoked per day (≤10, 11-20, and ≥21 cigarettes/d) in all analyses. The cutoff for duration of quit used to define smoking status was derived by first modeling more detailed intervals of quit duration and collapsing adjacent categories with similar effect estimates. A similar approach was used to define the variables of smoking duration and intensity. The potential confounding effects of passive smoking (defined as ≥5 years of exposure to secondhand smoke), rigorous physical activity [continuous metabolic equivalent (MET)-based score], total intake (in quartiles) of energy, grams of fat, meat, fish, fruits and vegetables, as well as use of multivitamins (any use versus no use) were explored. Thus, 70,010 men (196 lung cancer cases) with complete data for these covariates were included in this analysis.

We also examined the relationships between alcoholic beverage consumption and lung cancer among smokers in stratified analyses restricted to (*a*) ever-smokers and (*b*) smokers who smoked at least 20 pack-years in their lifetime. To further eliminate the possibility of residual confounding by race, we also performed stratified analyses restricted to Whites. In addition to overall lung cancer risk, adenocarcinoma of the lung (n = 132) was examined separately, as this type of lung cancer might have a different etiology from that of squamous cell carcinoma and small cell lung cancer. We did not identify enough squamous cell carcinoma (n = 21) and small cell/neuroendocrine lung cancers (n = 18) to conduct separate analyses for these histologic types. All analyses were conducted using SAS statistical software version 9 (Statistical Analyses System).

Results

The 78,168 men in these analyses contributed 300,516 person-years between 2002 and 2006. The distribution of baseline characteristics by lung cancer status is shown in Table 1. In the crude analysis, liquor intake was positively associated with lung cancer risk, whereas red wine intake was inversely associated with lung cancer risk. Age, race/ethnicity, education, household income, history of COPD/emphysema, cigarette smoking, passive smoking, vigorous physical activity, fish and fruit/vegetable consumption, as well as use of multivitamins also were associated significantly with lung cancer status.

Table 2 presents baseline characteristics by alcoholic beverage type and level of consumption. Age, race/ethnicity, income, education, BMI, vigorous physical activity, history of COPD/emphysema, smoking, and dietary intake were significantly associated with levels of consumption for each of the four alcoholic beverage types. Current smoking was positively associated with increased beer and liquor consumption but was inversely associated with red wine and white wine use. All four types of alcoholic beverages were associated with increase calorie intake. Beer and liquor drinking were also associated with greater meat intake, whereas reduced meat consumption was found with wine drinking. Use of red wine also appeared to be associated with increased intake of fruits and vegetables.

We did not find any clear association between risk of lung cancer and beer, white wine, and liquor consumption. Hazard ratio [HR; 95% confidence interval (95% CI)] estimates for consuming at least 1 drink/d of beer, white wine, and liquor were 0.78 (0.45-1.35), 0.87 (0.31-2.40), and 0.93 (0.54-1.58), respectively (Table 3). An inverse association for red wine intake, however, was suggested by the linear model in which level of red wine intake was modeled as a continuous variable (P = 0.06; Table 3). Adjusting for passive smoking, BMI, vigorous physical activity, intake of total calories, fat, meat, fish, fruit, and vegetable, and use of multivitamins did not affect the effect estimates. A significant association was found for beer intake of <1 drink/wk [HR (95% CI), 1.48 (1.00-2.19)]; however, there was no clear dose-response relationship. Because we did not find strong heterogeneity in the associations for beer, white wine, and liquor, the effect of combined consumption of these three types of alcoholic beverages was examined. Again, we did not find any clear association for the combined alcohol intake. The HR (95% CI) estimates for combined alcohol intake of <1 drink/d, 1 to <2 drinks/d, 2 to < 3 drinks/d, and ≥ 3 drinks/d are 1.26 (0.87-1.83), 0.71 (0.36-1.39), 0.96 (0.50-1.87), and 1.08 (0.60-1.94), respectively.

Among ever-smokers (191 lung cancer cases, 169,812 person-years), consumption of at least 1 drink of red wine per day was associated with an approximately 60% reduced risk of lung cancer [HR (95% CI), 0.39 (0.14-1.08)]. An inverse association between red wine intake and lung cancer was also indicated by test of linear trend (P = 0.03; Table 4), and a one-drink increase in red wine per month was associated with 2% reduction in lung cancer risk [HR (95% CI), 0.98 (0.96-1.00)]. A slightly stronger association for red wine was observed among ever-smokers who smoked at least 20 pack-years in their lifetime (135 lung cancer cases, 47,074 person-years). The HR (95% CI) for one-drink increase of red wine per month among this group was 0.96 (0.93-1.00; P = 0.04). Again, no clear association between lung cancer risk and beer, white wine, or liquor consumption was observed in these stratified analyses. Similar lung cancer HRs for each type of alcoholic beverage consumption were also observed in analyses conducted exclusively among Whites, restricted or unrestricted by smoking status. When we separately examined the cases of adenocarcinoma of the lung, a significant inverse association for red wine was still observed, particularly among ever-smokers (Table 5).

Discussion

In this multiethnic cohort of Californian men, we did not find any clear association between lung cancer risk and consumption of beer, white wine, or liquor after adjusting for demographics and lifestyle factors including smoking history, socioeconomic status, BMI, and history of COPD/emphysema. However, an inverse association for red wine use was consistently observed, particularly among ever-smokers.

Alcohol consumption has been shown to increase risk for several cancers, including cancers of the head and neck, esophagus, liver, colon, rectum, and female breast (15). The carcinogenic mechanism of alcohol consumption may involve the generation of acetaldehyde and oxidative stress during the metabolism of ethanol (16) and/or through the carcinogenic contaminants found in alcoholic beverages such as nitrosamines and polycyclic aromatic hydrocarbons (17-19). The effect of alcohol use on lung cancer, however, has been controversial. Previous studies have reported inconsistent findings possibly due to various degrees of residual confounding and true heterogeneity by types and levels of alcoholic beverage used between study populations (5, 20-27). A recent meta-analysis reported positive associations for beer and liquor consumption of ≥1 drink/d and inverse association for wine intake (28). However, the effect of residual confounding cannot be excluded from these findings because many of the previous studies only performed minimal adjustment for smoking and still more did not consider other potential confounders.

In this study, we carefully addressed the concern of confounding by tobacco smoking by taking into account

Table 1. Baseline characteristics by lung cancer status

	Mean (SD) or *n* (%)*		*P*
	Noncases (*n* = 77,958)	Lung cancer (*n* = 210)	
Age at baseline (y)	58.2 (7.1)	63.5 (5.5)	<0.01
Ethnicity			
White	48,344 (62.0)	142 (67.6)	<0.01
African American	5,922 (7.6)	27 (12.9)	
Hispanic	6,761 (8.7)	18 (8.6)	
Asian	11,263 (11.5)	17 (8.1)	
Other	5,157 (6.6)	6 (2.9)	
Education			
Less than college	41,113 (52.7)	148 (70.5)	<0.01
College or higher	36,129 (46.3)	62 (29.5)	
Household income			
$0-40,000	11,523 (19.9)	57 (27.1)	<0.01
$40,000-80,000	28,447 (36.5)	94 (44.8)	
>$80,000	30,841 (39.6)	54 (25.7)	
History of COPD/emphysema			
No	76,736 (98.4)	181 (86.2)	<0.01
Yes	1,222 (1.6)	29 (13.8)	
Cigarette smoking			
Never-smokers (%)	33,517 (43.0)	19 (9.1)	<0.01
Former smokers (%)	35,206 (45.2)	104 (49.5)	
Current smokers (%)	9,200 (11.8)	87 (41.4)	
Pack-years (former and current smokers)	17.2 (20.0)	37.5 (27.2)	
Passive smoking			
No	7,420 (9.5)	8 (3.8)	0.02
Yes	69,293 (88.9)	199 (94.8)	
BMI			
Underweight (BMI < 18.5)	3,126 (4.0)	9 (4.3)	0.04
Normal weight (18.5 ≤ BMI < 25)	19,226 (24.7)	68 (32.4)	
Overweight (25 ≤ BMI < 30)	35,261 (45.2)	85 (40.5)	
Obese (BMI ≥ 30)	20,345 (26.1)	48 (22.9)	
Vigorous activity score†	612.9 (1214.9)	266.3 (688.6)	<0.01
Alcohol intake (servings/mo)			
Total alcohol	23.3 (44.1)	24.0 (45.0)	0.81
Beer	9.4 (27.3)	10.4 (31.5)	0.60
Red wine	5.5 (16.0)	2.7 (9.0)	<0.01
White wine, including rosé	3.3 (12.4)	2.3 (8.3)	0.25
Liquor	5.1 (19.0)	8.7 (28.4)	<0.01
Dietary intake			
Total calories (kcal/d)	2,072.0 (1,120.5)	1,938.3 (865.2)	0.07
Fat (g/d)	81.1 (52.3)	79.1 (43.5)	0.58
Meat (servings/mo)	34.1 (29.1)	37.3 (29.3)	0.10
Fish (servings/mo)	8.4 (10.6)	6.8 (7.3)	0.02
Fruits/vegetables (servings/d)	4.2 (3.1)	3.4 (2.3)	<0.01
Use multivitamins (yes/no)			
No	31,707 (40.7)	102 (48.6)	0.02
Yes	46,251 (59.3)	108 (51.4)	

*Percentage may not add up to 100% due to missing values.
†Vigorous activity was defined as a minimum of 1,260 MET-h activity per week on average, equivalent to at least 3.5 h of activity with a minimum MET level of 6. Scores were derived by multiplying assigned MET values by duration and frequency and summing across activity.

the smoking status, duration of quit, intensity of daily smoking, as well as number of years as a smoker. A previous study showed that adjusting for intensity and duration as separate variables led to better model fit than in a model using only pack-years (29). Adjusting for smoking status is also essential to distinguish the qualitative difference between never- and ever-smokers from the quantitative effect of smoking (29). This was assessed and confirmed in our study using global model fit statistics.

In addition to tobacco smoking, alcoholic beverage consumption also was associated with other lung cancer-related demographic and lifestyle factors. Our findings are consistent with previous studies that, in the United States, red wine drinkers are less likely be to current smokers (6, 8). Red wine users also consume more fruit and vegetables compared with people who use the other types of alcoholic beverage or nondrinkers (6, 8). Our results further indicate that the association with potential confounders may not be monotonic across levels of alcoholic beverage intake. For example, we found that occasional beer and liquor drinkers tend to have higher income and education compared with nondrinkers or moderate drinkers (but this is not seen for red and white wine; see Table 2). This finding suggests that light drinkers may be different in many ways from nondrinkers and moderate drinkers in terms of socio-economic status and health-related lifestyle choices. Therefore, it may be important to include sufficiently detailed categories of alcohol drinking and covariates to achieve better control of confounding especially in the presence of strong confounders. Importantly, we explored

Table 2. Selected baseline characteristics by level of alcoholic beverage consumption

	n (%)			
	Nondrinkers	<1 drink/wk	≥1 drink/wk, <1 drink/d	≥1 drink/d
Beer				
No. men	34,059	20,365	16,832	6,786
Age, mean (SD)*	58.7 (7.1)	58.1 (7.1)	57.6 (7.0)	57.6 (6.9)
White race (%)*	59.3	59.0	68.3	69.7
Annual income ≥$80,000 (%)*	35.0	42.6	46.0	37.0
College education (%)*	44.5	49.1	50.1	38.2
BMI, mean (SD)*	28.2 (5.3)	28.0 (4.8)	27.6 (4.4)	27.3 (4.3)
Rigorous physical activity (MET), mean (SD)*	560.6 (1,196.6)	609.9 (1,175.1)	715.6 (1,272.4)	621.2 (1,255.2)
History of COPD/emphysema (%)*	2.0	1.3	1.1	1.9
Tobacco smoking*				
Never-smokers (%)	45.9	44.2	41.1	28.9
Former smokers (%)	42.4	44.8	48.3	52.6
Current smokers (%)	11.7	11.1	10.6	18.5
Pack-years (current and former smokers), mean (SD)	18.6	8.9 (16.3)	8.5 (15.1)	14.1 (20.3)
Passive smoking ≥5 y (%)	87.1	89.2	90.2	93.8
Dietary intake*				
Total calories (kcal/d), mean (SD)	1,961.1 (1,051.8)	2,030.6 (1,099.2)	2,227.45 (973.8)	2,604.7 (1,358.9)
Meat (servings/mo), mean (SD)	33.0 (28.9)	33.5 (28.6)	35.7 (26.2)	40.8 (3.0)
Fish (servings/mo), mean (SD)	7.9 (10.2)	8.7 (10.5)	9.0 (9.4)	8.6 (10.7)
Fruits/vegetables (servings/d), mean (SD)	4.1 (3.2)	4.3 (3.1)	4.4 (2.9)	4.0 (3.1)
Use of multivitamin (yes/no), %	58.8	60.7	60.1	56.1
Red wine				
No. men	39,585	19,518	14,414	4,528
Age, mean (SD)*	58.1 (7.2)	57.8 (7.1)	58.5 (6.9)	59.6 (6.5)
White race (%)*	57.1	57.5	75.8	81.6
Annual income ≥$80,000 (%)*	31.9	41.4	53.7	52.7
College education (%)*	37.9	48.5	61.7	61.7
BMI, mean (SD)*	28.3 (5.2)	28.0 (4.8)	27.2 (4.2)	27.0 (3.9)
Rigorous physical activity (MET), mean (SD)*	516.0 (1,171.0)	618.6 (1,191.6)	794.8 (1,275.9)	840.1 (1,369.3)
History of COPD/emphysema (%)*	2.1	1.2	1.0	1.2
Tobacco smoking*				
Never-smokers (%)	42.7	43.5	44.7	36.2
Former smokers (%)	43.2	44.9	47.8	55.3
Current smokers (%)	14.0	11.6	7.5	8.4
Pack-years (current and former smokers), mean (SD)	11.3 (19.1)	8.9 (16.1)	8.0 (14.6)	10.5 (16.9)
Passive smoking ≥5 y (%)	88.5	89.3	88.8	91.5
Dietary intake*				
Total calories (kcal/d), mean (SD)	2,016.2 (1,103.2)	2,092.2 (1,157.0)	2,208.2 (948.4)	2,408.6 (1,106.0)
Meat (servings/mo), mean (SD)	35.0 (30.1)	34.6 (29.6)	33.2 (24.7)	33.1 (25.0)
Fish (servings/mo), mean (SD)	7.3 (10.0)	8.8 (10.4)	10.0 (9.6)	10.8 (11.5)
Fruits/vegetables (servings/d), mean (SD)	3.9 (3.1)	4.2 (3.1)	4.8 (2.9)	5.0 (3.3)
Use of multivitamin (yes/no, %)	56.6	61.0	63.9	61.0
White wine				
No. men	45,148	20,637	10,062	2,116
Age, mean (SD)*	58.1 (7.1)	58.0 (7.1)	58.8 (6.8)	59.9 (6.4)
White race (%)*	58.0	60.7	78.6	83.2
Annual income ≥$80,000 (%)*	33.6	43.7	54.5	54.7
College education (%)*	39.9	50.2	63.6	63.7
BMI, mean (SD)*	28.1 (5.1)	28.0 (4.8)	27.2 (4.1)	27.2 (3.9)
Rigorous physical activity (MET), mean (SD)*	552.9 (1,191.0)	637.9 (1,200.2)	791.4 (1,277.7)	745.7 (1,403.6)
History of COPD/emphysema (%)*	1.9	1.3	1.2	1.3
Tobacco smoking*				
Never-smokers (%)	42.0	44.1	45.6	37.2
Former smokers (%)	44.3	45.2	47.3	53.8
Current smokers (%)	13.6	10.7	7.0	8.9
Pack-years (current and former smokers), mean (SD)	11.1 (18.7)	8.5 (15.7)	8.0 (15.1)	11.4 (17.5)
Passive smoking ≥5 y (%)	88.5	89.4	89.2	92.4
Dietary intake*				
Total calories (kcal/d), mean (SD)	2,011.8 (1,078.8)	2,139.0 (1,144.7)	2,284.4 (952.7)	2,464.2 (1,337.1)
Meat (servings/mo), mean (SD)	34.2 (29.2)	34.8 (29.1)	34.5 (25.3)	35.7 (29.8)
Fish (servings/mo), mean (SD)	7.6 (10.1)	8.9 (10.3)	10.3 (9.7)	10.3 (11.4)
Fruits/vegetables (servings/d), mean (SD)	4.0 (3.1)	4.4 (3.1)	4.8 (2.9)	4.5 (3.1)
Use of multivitamin (yes/no, %)	57.3	61.5	63.2	62.6
Liquor				
No. men	45,513	19,289	9,269	3,942
Age, mean (SD)*	58.4 (7.1)	57.4 (7.1)	58.2 (7.0)	60.1 (6.7)
White race (%)*	60.5	58.6	69.8	78.7
Annual income ≥$80,000 (%)*	36.4	42.8	46.9	42.3

(*Continued on the following page*)

Table 2. Selected baseline characteristics by level of alcoholic beverage consumption (Cont'd)

	n (%)			
	Nondrinkers	<1 drink/wk	≥1 drink/wk, <1 drink/d	≥1 drink/d
College education (%)*	45.2	47.0	50.4	46.4
BMI, mean (SD)†	27.8 (5.0)	28.1 (4.8)	28.0 (4.5)	28.1 (4.6)
Rigorous physical activity (MET), mean (SD)*	600.6 (1,226.3)	632.9 (1,196.8)	666.9 (1,239.7)	516.7 (1,091.2)
History of COPD/emphysema (%)*	1.7	1.3	1.4	2.1
Tobacco smoking*				
Never-smokers (%)	45.5	43.4	37.5	24.1
Former smokers (%)	43.4	45.1	49.8	55.0
Current smokers (%)	11.1	11.4	12.7	21.0
Pack-years (current and former smokers), mean (SD)	9.9 (17.8)	8.6 (15.7)	10.0 (16.3)	17.7 (21.9)
Passive smoking ≥5 y (%)	87.5	89.8	91.6	94.8
Dietary intake*				
Total calories (kcal/d), mean (SD)	2,001.7 (1,030.0)	2,137.8 (1,150.4)	2,278.0 (1,029.8)	2,499.6 (1,457.6)
Meat (servings/mo), mean (SD)	32.7 (27.7)	35.2 (29.1)	37.9 (29.1)	41.7 (34.6)
Fish (servings/mo), mean (SD)	7.9 (9.9)	8.9 (10.4)	9.7 (10.2)	9.3 (11.3)
Fruits/vegetables (servings/d), mean (SD)	4.2 (3.1)	4.3 (3.0)	4.3 (2.8)	4.2 (3.4)
Use of multivitamin (yes/no, %)	58.4	60.7	61.1	58.5

*P value of χ^2 test across level of consumption was <0.01 for that type of alcoholic beverage.
†P value of χ^2 test for BMI across level of liquor consumption was 0.02.

the potential confounding effect of exposure to passive smoking, physical activity, and dietary intake including multivitamins use. However, none of these factors were found to materially affect the effect estimates of alcoholic beverage consumption despite their strong association with alcohol use.

Adjusting for demographic characteristics and lifestyle factors including smoking history, socioeconomic status, BMI, and history of COPD/emphysema, we did not find any clear adverse effect of alcoholic beverage consumption on the risk of lung cancer. We also did not observe any adverse effect of combined alcohol consumption from beer, white wine, and liquor for up to 3 drinks/d. This finding is consistent with a previous meta-analysis that reported no clear association between total alcohol intake and lung cancer, except at a very high level of consumption of approximately ≥5 drinks/d (30). A pooled analysis reported slightly increased risk for consuming ≥30 g/d alcohol (a standard drink contains ~13 g alcohol) in both men and women [relative risk (95% CI), 1.21 (0.91-1.61) for men and 1.16 (0.94-1.43) for women], albeit the 95% CI included 1 (4). However, given our observation of the inverse association for red wine, the effect estimate for total alcohol intake may be misleading due to potential effect heterogeneity among alcoholic beverage types.

We observed an inverse association between red wine intake and risk of lung cancer among ever-smokers, with a stronger association seen among those who smoked ≥20 pack-years in their lifetime. This finding, if confirmed, is of interest for lung cancer chemoprevention in current and former smokers. Red wine is known to contain high levels of antioxidants such as flavonoids and resveratrol. The contrasting finding of red and white wine is particularly interesting. Use of white wine appears to have a similar pattern of associations with

Table 3. Adjusted HR (95% CI) for lung cancer by level of beer, red wine, white wine, and liquor consumption

	Frequency of consumption	Mean no. drinks/mo	Cases	Person-years	HR* (95%CI)	Linear*,† HR (95% CI)	$P_{\text{linear trend}}$
Beer	Nondrinker‡	0	94	130,678	1	1.00 (0.99-1.00)	0.42
	<1 drink/wk	1.3	64	78,956	1.48 (1.00-2.19)		
	≥1 drink/wk, <1 drink/d	11.2	34	64,458	1.04 (0.65-1.65)		
	≥1 drink/d	76.8	18	25,949	0.78 (0.45-1.35)		
Red wine	Nondrinker‡	0	127	152,007	1	0.98 (0.97-1.00)	0.06
	<1 drink/wk	1.1	55	75,780	1.15 (0.73-1.81)		
	≥1 drink/wk, <1 drink/d	11.1	21	55,023	0.65 (0.37-1.15)		
	≥1 drink/d	55.1	7	17,217	0.55 (0.23-1.29)		
White wine	Nondrinker‡	0	137	173,488	1	1.00 (0.98-1.01)	0.71
	<1 drink/wk	1.2	49	80,075	0.86 (0.54-1.37)		
	≥1 drink/wk, <1 drink/d	10.1	20	38,224	1.09 (0.62-1.92)		
	≥1 drink/d	60.4	4	7,960	0.87 (0.31-2.40)		
Liquor	Nondrinker‡	0	123	174,839	1	1.00 (1.00-1.01)	0.75
	<1 drink/wk	1.1	43	74,946	0.92 (0.60-1.42)		
	≥1 drink/wk, <1 drink/d	10.9	26	35,332	1.05 (0.64-1.71)		
	≥1 drink/d	69.8	18	14,815	0.93 (0.54-1.58)		

*Model adjusted for age, ethnicity, education, household income, BMI, smoking status (never, current, and past by quit duration), cigarettes smoked per day, smoking duration, and history of COPD/emphysema. Beer, red wine, white wine, and liquor consumption were mutually adjusted for in the model.
†Linear for one-drink increase per month.
‡May include occasional drinkers who drank <1 drink/mo.

Table 4. Adjusted HR (95% CI) for lung cancer by level of beer, red wine, white wine, and liquor consumption among ever-smokers

	Frequency of consumption	Mean no. drinks/mo	Cases	Person-years	HR* (95%CI)	Linear*,† HR (95% CI)	$P_{linear\ trend}$
Beer	Nondrinker‡	0	83	69,725	1	1.00 (0.99-1.00)	0.31
	<1 drink/wk	1.3	59	43,584	1.56 (1.04-2.36)		
	≥1 drink/wk, <1 drink/d	11.5	33	37,796	1.17 (0.73-1.89)		
	≥1 drink/d	80.9	16	18,380	0.74 (0.41-1.33)		
Red wine	Nondrinker‡	0	118	86,003	1	0.98 (0.96-1.00)	0.03
	<1 drink/wk	1.2	50	42,409	1.10 (0.68-1.78)		
	≥1 drink/wk, <1 drink/d	11.0	18	30,194	0.64 (0.35-1.17)		
	≥1 drink/d	57.3	5	10,924	0.39 (0.14-1.08)		
White wine	Nondrinker‡	0	127	99,434	1	1.00 (0.98-1.01)	0.71
	<1 drink/wk	1.2	45	44,291	0.83 (0.51-1.35)		
	≥1 drink/wk, <1 drink/d	10.2	15	20,707	0.86 (0.46-1.63)		
	≥1 drink/d	62.2	4	4,922	0.94 (0.34-2.62)		
Liquor	Nondrinker‡	0	108	94,149	1	1.00 (1.00-1.01)	0.72
	<1 drink/wk	1.1	42	42,075	1.06 (0.68-1.66)		
	≥1 drink/wk, <1 drink/d	11.2	23	21,970	1.05 (0.62-1.77)		
	≥1 drink/d	71.0	18	11,205	0.99 (0.57-1.70)		

*Model adjusted for age, ethnicity, education, household income, BMI, smoking status (current, and past by quit duration), cigarettes smoked per day, smoking duration, and history of COPD/emphysema. Beer, red wine, white wine, and liquor consumption were mutually adjusted for in the model.
†Linear for one-drink increase per month.
‡May include occasional drinkers who drank <1 drink/mo.

health-related lifestyle factors as red wine, including smoking, diet, education, and income. Although white wine also contains phytochemical compounds, the concentration and activity of these antioxidants is much lower in white wine compared with red wine (31-33). Although we cannot completely exclude the possibility of residual confounding, the lack of association for white wine lends support to a causal association for red wine and suggests that compounds that are present at high concentrations in red wine but not in white wine, beer, or liquors may be protective against lung carcinogenesis. For example, red wine is a rich source of resveratrol. In preclinical models of carcinogenesis, resveratrol is found to alter the activation of procarcinogens in human bronchial epithelial cells *in vitro* (34, 35), induce apoptosis in human lung cancer cell lines (36), and retard lung tumor growth in mice (37), suggesting the chemopreventive potential of resveratrol on lung cancer. Clinical studies will be needed to determine the effect of resveratrol from food source in humans. To our knowledge, there was only one other study that examined the effect of red wine and white wine separately. The authors reported an inverse association with lung cancer for red wine but a positive association for white wine (27).

There are several limitations in our study. First, we do not have long-term data on alcohol use, which limited our ability to study the effect of former drinking and the effect of alcoholic beverage consumption as a lung cancer initiator. However, some experimental evidence suggests that alcohol may act as a promoter in the late stage of carcinogenesis (38). Therefore, recent consumption patterns may be one of the relevant exposures to assess. However, if there was an association between former drinking and lung cancer risk, our results might be biased downward due to the potential inclusion of former drinkers in the reference group of ''nondrinkers.'' Second, members of the CMHS cohort on average reported moderate alcohol consumption. This limited our ability to examine the effect of heavy intake on risk of lung cancer. Third, we had few subjects with lung cancer who were never-smokers or had squamous cell histology, thus preventing the investigation of the effect of alcoholic beverage use in these subgroups. Despite these limitations, our study has several important strengths, including the availability of detailed information on

Table 5. Adjusted HR (95% CI) for lung adenocarcinoma by level of red wine consumption

Smoking status	Frequency of red wine consumption	Cases	HR (95% CI)	Linear* HR (95% CI)	$P_{linear\ trend}$
All (never + ever smokers)	Nondrinker†	79	1	0.98 (0.95-1.00)	0.08
	<1 drink/wk	37	1.25 (0.72-2.20)		
	≥1 drink/wk, <1 drink/d	12	0.50 (0.24-1.07)		
	≥1 drink/d	4	0.43 (0.13-1.42)		
Ever-smokers	Nondrinker†	73	1	0.96 (0.92-1.00)	0.03
	<1 drink/wk	32	1.14 (0.63-2.09)		
	≥1 drink/wk, <1 drink/d	9	0.44 (0.19-1.02)		
	≥1 drink/d	2	0.15 (0.02-1.11)		

NOTE: Model adjusted for age, ethnicity, education, household income, BMI, smoking status (never, current, and past by quit duration), cigarettes smoked per day, smoking duration, history of COPD/emphysema, and consumption of other alcoholic beverages (beer, white wine, and liquor).
*Linear for one-drink increase per month.
†May include occasional drinkers who drank less <1 drink/mo.

smoking, alcoholic beverage consumption and other lifestyle factors, comprehensive adjustment for confounding, and reliable and sensitive lung cancer ascertainment.

Our results did not support any adverse effect of moderate alcoholic beverage consumption on lung cancer risk in men, but these results cannot be extrapolated to heavy alcohol consumption. We observed an inverse association between red wine intake and risk of lung cancer among ever-smokers, which suggests further research into the lung cancer chemopreventive agents that occur in abundance in red wine. These findings, however, should be confirmed in future epidemiologic studies that separately examine the effect of red wine from other alcoholic beverages.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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