

## Alcohol Consumption and Risk of Lung Cancer: The Framingham Study

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**Background:** Reports on the association between alcohol consumption and the risk of lung cancer have been inconsistent. The purpose of this study was to assess this association in a cohort study. **Methods:** This study included 4265 participants in the original population-based Framingham Study cohort and 4973 subjects in the offspring cohort. Alcohol consumption data were collected periodically for both cohorts. We used the risk sets method to match control subjects to each case patient based on age, sex, smoking variables, and year of birth. We used a conditional logistic regression model to estimate the relative risk of lung cancer according to alcohol consumption. **Results:** Alcohol consumption was generally light to moderate (i.e., <12 g/day) in both cohorts. During mean follow-ups of 32.8 years in the original and 16.2 years in the offspring cohorts, 269 cases of lung cancer occurred. In categories of total alcohol consumption of 0, 0.1–12, 12.1–24, and greater than 24 g/day, the crude incidence rates of lung cancer were 7.4, 13.6, 16.4, and 25.2 cases per 10 000 person-years, respectively, in the original cohort and 6.6, 4.3, 7.9, and 12.3 cases per 10 000 person-years, respectively, in the offspring cohort. However, after adjustment for age, sex, pack-years of smoking, smoking status, and year of birth in a multivariable conditional logistic regression model, relative risks for lung cancer from the lowest to the highest category of alcohol consumption were 1.0 (referent), 1.0 (95% confidence interval [CI] = 0.5 to 2.1), 1.0 (95% CI = 0.5 to 2.3), and 1.1 (95% CI = 0.5 to 2.3), respectively, in the original cohort and 1.0, 1.4 (95% CI = 0.5

to 3.6), 1.1 (95% CI = 0.3 to 3.6), and 2.0 (95% CI = 0.7 to 5.7), respectively, in the offspring cohort. **Conclusion:** Alcohol consumption among subjects in the Framingham Study, most of whom were light to moderate drinkers, was not statistically significantly associated with the risk of lung cancer. [J Natl Cancer Inst 2002;94:1877–82]

Epidemiologic studies have reported inconsistent findings on the association between alcohol consumption and the risk of lung cancer. In a prospective study, Woodson et al. (1) found that alcohol consumption was not associated with lung cancer among male smokers. An earlier Framingham study that used alcohol information from the second biennial examination (from 1950 through 1954) of the original cohort showed that alcohol was associated with an increased risk for stomach cancer but not for other types of cancer (2). However, Prescott et al. (3) found

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that alcohol consumption was associated with an increased risk for lung cancer among men consuming at least 21 drinks per week. Several case-control studies have reported that alcohol consumption was associated with an increased risk for lung cancer (4–6). Inconsistency among studies that assessed the association between alcohol consumption and the risk of lung cancer may be partially explained in some studies by residual confounding by cigarette smoking, the major risk factor of lung cancer (7–10). Because alcohol consumption is positively associated with cigarette smoking, it is important to eliminate the confounding effect of smoking in a study assessing the effects of alcohol on the risk of lung cancer. In addition, little is known about the association between alcohol consumption and histologic types of lung cancer. The present study evaluated the association between total alcohol consumption and the risk of lung cancer among men and women participating in the Framingham Study.

## SUBJECTS AND METHODS

### Study Subjects

The Framingham Study is a population-based cohort study started in 1948 in Framingham, Massachusetts. The original cohort included 5209 participants, 28–62 years of age at the first examination. Survivors have been examined every 2 years since then. In 1971, 5124 children of the original cohort and their spouses were invited to participate in a prospective study, referred to as the Framingham Offspring Study. Since 1971, participants in the offspring cohort were reexamined 8 years after the first examination and every 4 years thereafter. During each clinic visit, participants of these two studies undergo a series of tests and examinations, including a detailed medical history, a physician-administered physical examination, and an assessment of blood parameters and cardiac and lung function. Noninvasive cardiovascular tests and series of laboratory tests are also obtained. Detailed descriptions of the Framingham Study have been published previously (11,12). Written informed consent was obtained from study participants, and the study protocol was approved by the Institutional Review Board of Boston Medical Center. This study included 4265 participants from the original cohort and 4973 subjects from the offspring cohort.

### Ascertainment of Lung Cancer

As described previously (13), cases of lung cancer were identified through self-report at clinic visits to the Framingham Study, by surveillance of hospitalizations at the only local hospital in Framingham, and by searching the National Death Index. For each suspected case of lung cancer, histopathologic reports were requested from the source of diagnosis (hospital and physicians' offices) and were reviewed along with the subject's chart to determine the date of diagnosis and the classification according to the International Classification of Diseases in Oncology [topography code 162 (14)]. Based on histopathology, lung cancers were further grouped into the following three major categories: squamous cell carcinoma, adenocarcinoma, and other types. For multiple occurrences of lung cancer, only the first diagnosis was considered for these analyses.

### Alcohol Consumption

Information on alcohol consumption has been collected repeatedly from both the original and offspring cohorts. At two

early examinations (examinations 2 and 7) of the original cohort, subjects were asked how many 2-ounce cocktails, 8-ounce glasses of beer, and 4-ounce glasses of wine they consumed in a month. At subsequent examinations (examinations 12–15 and 17–23) of the original cohort and at all examinations (examinations 1–6) of the offspring cohort, subjects were asked about the number of 1.5-ounce cocktails, 12-ounce glasses (or cans) of beer, and 5-ounce glasses of wine they consumed in a week. Total alcohol consumption (g/day) was computed by multiplying the average content of alcohol in beer, wine, and mixed drinks times the number of drinks consumed. Because there was a secular change in the alcohol content of liquor commonly consumed (from 100 proof to 80 proof) and the type of wine generally consumed (from fortified to table wine), as well as a change in the average serving sizes of drinks, we used two different conversion formulas to calculate the total ethanol content according to when the data were collected. For examinations 2 and 7 of the original cohort, the total ethanol content (g/day) was calculated as  $([1.0 \times \text{the number of cocktails per month}] + [0.4 \times \text{the number of beers per month}] + [0.67 \times \text{the number of glasses of wine per month}]) \times 28.35/30$ ; the latter term represents 28.35 g of alcohol per fluid ounce divided by 30 days in a month. For all later examinations in the original cohort and all examinations in the offspring cohort, the ethanol intake per day was estimated as  $([0.57 \times \text{the number of cocktails per week}] + [0.44 \times \text{the number of beers per week}] + [0.40 \times \text{the number of glasses of wine per week}]) \times 28.35/7$ ; the latter term represents 28.35 g of alcohol per fluid ounce divided by 7 days in a week.

### Other Variables

Information on smoking was collected at each examination with standardized questionnaires administered by the examining physician. Each subject was asked if he or she smoked cigarettes. If the answer was yes, the average number of cigarettes smoked per day was recorded. Current nonsmokers were asked if they had ever smoked in the past; a positive answer was used to classify former smokers. To calculate pack-years of smoking, the average number of cigarettes smoked per day was divided by 20 and then multiplied by the number of years of cigarette smoking.

Information on education was self-reported.

### Statistical Analysis

Of the 5209 subjects in the original cohort, we excluded 944 subjects because of missing data on smoking pack-years from 534 subjects or smoking status from 50 subjects or alcohol intake from 360 subjects. Of the 5124 subjects in the offspring cohort, 151 subjects were excluded because of missing data on smoking pack-years (from 42 subjects) or alcohol intake (from 109 subjects). All analyses were conducted initially within each cohort separately and combined after observing that the findings were similar in the original and the offspring cohorts.

We used the risk sets method (15) to control for confounding by smoking, age, sex, and year of birth. For each case patient with lung cancer, all subjects who were free of lung cancer at the time of the case patient's diagnosis and who met the matching criteria (matched to the case patient by age [ $\pm 2$  years], pack-years of cigarette smoking [ $\pm 2$  pack-years], sex, year of birth [ $\pm 2$  years], and smoking status [never, former, and current smokers]) were used as control subjects. The median number of control subjects per case patient was 3 (range = 1–156). For case

patients who were former smokers, control subjects were also matched on the number of years since the case patient quit smoking ( $\pm 2$  years). Each case patient and all of his or her matching control subjects constituted a risk set. Control subjects could be included in more than one risk set, and case patients could be included in risk sets as control subjects for case patients with earlier lung cancer diagnoses.

Alcohol consumption was categorized as follows: 0, 0.1–12, 12.1–24, and greater than 24 g/day (one “drink” is about 12 g of alcohol). Because alcohol data were not collected at every examination in the cohort study, for each risk set, total alcohol intake for each subject was computed as a weighted average of reported alcohol intake from examination 2 until the examination preceding the case patient’s diagnosis, with weights proportional to the time interval between reports of alcohol consumption. Within a risk set, pack-years of cigarette smoking were averaged across examinations from the first until the last examination preceding the diagnosis of lung cancer in the case patient. Person-years of follow-up were calculated from baseline until 1) the first occurrence of lung cancer, 2) loss to follow-up, or 3) the end of the study period. Crude incidence rates were computed by dividing the number of case patients with lung cancer by the number of person-years of follow-up in the corresponding alcohol category.

We used conditional logistic regression models to estimate the adjusted relative risk of lung cancer adjusting for age, year of birth, sex, pack-years of smoking, and smoking status. In this regression analysis, each risk set was treated as a stratum. We modeled alcohol intake as a series of indicator variables. We also evaluated education as a proxy to assess the effect of socioeconomic status on the association between alcohol consumption and lung cancer. Subjects were categorized as having less than a high school education, being a high-school graduate, or having some college and higher, and indicator variables were included in the regression models. However, additional adjustment for education in the conditional logistic regression model did not change the results, and so education was not included in the final model. We also used an unrestricted quadratic spline to assess a dose–response relationship between alcohol intake and the risk of lung cancer. Knots were set at 6, 12, and 24 g of alcohol per day.

## RESULTS

During a mean follow-up of 32.8 years (range = 17.0–48.2 years), 194 case patients with lung cancer were identified in the original cohort (123 men and 71 women). Among these lung cancers, 52 were adenocarcinoma, 56 were squamous cell carcinoma, and 86 were other histologic types of lung cancer. In the offspring cohort with a mean follow-up of 16.2 years (range = 0.8–24.6 years), 75 case patients with lung cancer were identified (37 men and 38 women). Of these lung cancers, 25 were adenocarcinoma, 21 were squamous cell carcinoma, and 29 were other histologic types of cancer. Thus, a total of 269 cases of lung cancer occurred during follow-up.

Baseline characteristics of the 9238 subjects who were eligible to be included in the analysis are presented in Table 1. In the original cohort, the 194 subjects who became case patients smoked more cigarettes and consumed more alcohol than did the control subjects. Case patients were more likely to be male, heavy smokers, and less educated, and were slightly younger than control subjects. Similar to the original cohort, case patients

in the offspring cohort smoked more, consumed more alcohol, and were less educated than control subjects (Table 1). However, unlike the original cohort, offspring case patients were about 5 years older than control subjects.

Characteristics of the study population according to their reported alcohol consumption at the first examination are shown in Table 2. In both cohorts, alcohol consumption was generally light to moderate and was strongly and positively associated with cigarette smoking and male sex.

The association of alcohol consumption with the risk of lung cancer is shown in Table 3. In the crude analysis, alcohol consumption was associated with an increased risk of lung cancer in both cohorts. Specifically, in categories of total alcohol consumption of 0, 0.1–12, 12.1–24, and greater than 24 g/day, the crude incidence rates of lung cancer were 7.4, 13.6, 16.4, and 25.2 cases per 10 000 person-years, respectively, in the original cohort and 6.6, 4.3, 7.9, and 12.3 cases per 10 000 person-years, respectively, in the offspring cohort. However, after adjustment for age, sex, pack-years of cigarette smoking, smoking status, and year of birth, alcohol consumption was no longer statistically significantly associated with the risk of lung cancer. From the lowest to the highest category of alcohol consumption, relative risks of lung cancer were 1.0 (reference), 1.0 (95% confidence interval [CI] = 0.5 to 2.1), 1.0 (95% CI = 0.5 to 2.3), and 1.1 (95% CI = 0.5 to 2.3), respectively, in the original cohort. In the offspring cohort, corresponding relative risks were 1.0 (reference), 1.4 (95% CI = 0.5 to 3.6), and 1.1 (95% CI = 0.3 to 3.6), respectively, for the first three alcohol categories. In the highest category of alcohol consumption, we observed an increased risk of lung cancer, but the CI was wide and the asso-

**Table 1.** Baseline characteristics of the study participants from the Framingham Study\*

Characteristics	Case patients	Control subjects
Cohort, No.	194	4071
Male, %	63.4	40.3
Age at baseline, y	41.6 $\pm$ 7.8	44.0 $\pm$ 8.6
Year of birth	1908 $\pm$ 8	1906 $\pm$ 9
Baseline alcohol intake, g/day	23.6 $\pm$ 39.2	13.4 $\pm$ 26.7
Cigarette smoking		
No. per day	20.4 $\pm$ 11.5	9.7 $\pm$ 11.9
No. of pack-years	24.7 $\pm$ 18.2	11.3 $\pm$ 16.4
Never smokers, %	8.8	44.4
Former smokers, %	0.5	2.0
Current smokers, %	90.7	53.6
Education		
Less than high school, %	29.2	29.0
High-school graduate, %	49.0	42.6
College and higher, %	21.8	28.4
Offspring, No.	75	4898
Male, %	49.3	47.2
Age at baseline, y	60.6 $\pm$ 13.1	55.2 $\pm$ 16.9
Year at birth	1912 $\pm$ 14	1918 $\pm$ 17
Baseline alcohol intake, g/day	25.1 $\pm$ 30.8	14.6 $\pm$ 20.3
Cigarette smoking		
No. per day	28.5 $\pm$ 15.7	13.7 $\pm$ 14.6
No. of pack-years	37.4 $\pm$ 24.0	12.3 $\pm$ 17.3
Never smokers, %	8.0	37.3
Former smokers, %	8.0	19.0
Current smokers, %	84.0	43.7
Education		
Less than high school, %	34.2	11.9
High-school graduate, %	60.5	73.2
College and higher, %	5.3	14.9

\*Data are presented as mean  $\pm$  standard deviation, unless otherwise indicated.

**Table 2.** Characteristics of the Framingham Heart Study population according to baseline alcohol intake\*

Characteristics	Baseline ethanol intake, g/day			
	0	0.1–12	12.1–24	>24
Cohort, No.	1378	1665	435	787
Male, %	24.5	37.0	54.5	72.9
Age at baseline, y	45.9 ± 8.6	43.0 ± 8.5	42.0 ± 8.2	43.3 ± 8.1
Year of birth	1904 ± 9	1907 ± 9	1908 ± 8	1906 ± 8
Cigarette smoking				
No. per day	5.4 ± 9.8	9.7 ± 11.2	13.2 ± 12.0	17.9 ± 13.3
Pack-years, No.	6.0 ± 13.4	10.7 ± 15.2	14.8 ± 15.2	23.0 ± 19.7
Never smokers, %	66.2	40.4	26.9	15.8
Former smokers, %	1.1	1.9	2.5	3.2
Current smokers, %	32.7	57.7	70.6	81.1
Education				
Less than high school, %	32.2	29.4	21.3	27.3
High-school graduate, %	43.0	43.9	40.4	42.7
College and higher, %	24.8	26.7	38.3	30.0
Offspring, No.	757	2381	865	970
Male, %	43.1	42.8	50.4	58.8
Age at baseline, y	54.6 ± 17.9	55.3 ± 17.3	55.5 ± 16.3	55.9 ± 15.3
Year of birth	1918 ± 18	1918 ± 18	1918 ± 17	1917 ± 16
Cigarette smoking				
No. per day	10.3 ± 14.1	11.8 ± 13.4	15.0 ± 13.9	21.3 ± 16.6
Pack-years, No.	9.3 ± 16.0	9.6 ± 14.6	13.4 ± 17.0	22.3 ± 22.4
Never smokers, %	54.0	41.1	29.3	19.8
Former smokers, %	12.6	17.0	21.7	25.7
Current smokers, %	33.4	41.9	49.0	54.5
Education				
Less than high school, %	15.4	11.3	28.6	24.2
High-school graduate, %	73.1	74.8	57.1	66.7
College and higher, %	11.5	13.9	14.3	9.1

\*Data are presented as mean ± standard deviation, unless otherwise indicated.

**Table 3.** Relation between average alcohol consumption and risk of lung cancer in the Framingham Study population

Average alcohol intake, g/day	No. of case patients with lung cancer*	Crude incidence rate, No. of case patients/10 000 person-years	Adjusted rate ratio† (95% CI)
<b>Original cohort</b>			
0	33	7.4	1.0 (reference)
0.1–12	77	13.6	1.0 (0.5 to 2.1)
12.1–24	24	16.4	1.0 (0.5 to 2.3)
>24	60	25.2	1.1 (0.5 to 2.3)
<b>Offspring cohort</b>			
0	11	6.6	1.0 (reference)
0.1–12	23	4.3	1.4 (0.5 to 3.6)
12.1–24	15	7.9	1.1 (0.3 to 3.6)
>24	26	12.3	2.0 (0.7 to 5.7)
<b>Both cohorts combined</b>			
0	44	7.2	1.0 (reference)
0.1–12	100	9.0	1.2 (0.7 to 2.1)
12.1–24	39	11.6	1.1 (0.6 to 2.1)
>24	86	19.1	1.3 (0.7 to 2.4)

\*Because of the lack of appropriate matched controls subjects, only 212 case patients were used in the adjusted analysis. CI = confidence interval.

†Adjusted for age, sex, smoking status, pack-years of cigarette smoking, and year of birth.

ciation was not statistically significant (relative risk = 2.0 [95% CI = 0.7 to 5.7]). An additional adjustment for education did not alter these findings. Combining both cohorts did not alter the results substantially. Because 42 case patients from the original cohort and 14 case patients from the offspring cohort did not have appropriate matched control subjects in the risk sets

method, we repeated the analyses with relaxed matching criteria to allow those case patients to have at least one control subject. Specifically, control subjects were matched on each case patient based on age ( $\pm 5$  years), sex, and pack-years of smoking ( $\pm 5$  pack-years). These additional analyses did not change the results (data not shown). Results from a quadratic spline did not show evidence for a dose–response relationship between alcohol intake and lung cancer risk (data not shown).

We evaluated whether the association between alcohol consumption and the risk of lung cancer differed by histologic type of lung cancer in the combined cohorts. In the crude analysis, higher levels of alcohol consumption were associated with an increased risk of all types of lung cancer. From the lowest to the highest category of alcohol intake, multivariable adjusted relative risks were 1.0, 2.9 (95% CI = 0.8 to 10.9), 1.5 (95% CI = 0.3 to 8.1), and 2.3 (95% CI = 0.5 to 10.5), respectively, for adenocarcinoma; 1.0, 0.4 (95% CI = 0.1 to 2.0), 0.4 (95% CI = 0.1 to 2.6), and 0.3 (95% CI = 0.1 to 1.7), respectively, for squamous cell carcinoma; and 1.0, 0.7 (95% CI = 0.2 to 2.3), 0.8 (95% CI = 0.2 to 2.9), and 0.8 (95% CI = 0.2 to 2.7), respectively, for all other types of lung cancer. Inferences from these data are difficult, however, because we had a limited number of case patients and the point estimates had wide 95% CIs. Furthermore, no trends were apparent in these analyses. Additional adjustment for education did not change these results.

## DISCUSSION

In this study, alcohol consumption was positively related to the risk of lung cancer in the crude analysis. However, after adjustment for pack-years of cigarette smoking and other major risk factors, we did not find evidence for a statistically signifi-

cant association between alcohol consumption and lung cancer in the original cohort and in the category of 0.1–24 g of alcohol per day in the offspring cohort. There was suggestive evidence for an increased risk of lung cancer with alcohol consumption greater than 24 g/day in the offspring cohort. Although an underestimation of smoking habits in the offspring cohort (from more intensive antismoking efforts in recent years) may have led to inadequate control of confounding in this group, the 95% CI was wide, and the findings may well result from chance. In addition, no dose–response relationship was observed between the amount of alcohol consumed and the risk of lung cancer.

Although moderate alcohol consumption has been inversely related to cardiovascular (16), all-cause (17), and cancer (17) mortality in some studies, data on the association between moderate alcohol consumption and risk of lung cancer in a community-based population have been inconsistent. Our findings are consistent with those studies that did not find an increased risk of lung cancer with alcohol consumption (1,2,18–21). Results from a meta-analysis indicated the lack of an association between alcohol consumption and lung cancer at lower levels of alcohol consumption (less than 2000 g/month) after adjustment for smoking and an increased risk of lung cancer with consumption of greater than 2000 g/month, the equivalent of more than 5 “drinks” per day (22).

Studies of heavy drinkers (3,23,24) and several epidemiologic studies (4–6) have reported a positive relationship between alcohol consumption and lung cancer. The discrepancy between these positive studies and our study could be explained partially by several limitations among studies. First, our study included few heavy drinkers, because most of the subjects consumed alcohol moderately. Second, residual confounding by smoking—a major confounder of the association between alcohol consumption and the risk of lung cancer (21,25)—may partially account for some of the inconsistencies. Third, because drinking patterns may change over time (26), the use of a single measurement of alcohol intake (baseline value) might introduce bias. Fourth, for case–control studies, selection bias and recall bias are inherent issues of the study design and could be very difficult to eliminate. Fifth, different lengths of follow-up time may also play a role. Our study used the risk sets method to match each case patient with lung cancer to control subjects on key potentially confounding factors.

In a secondary analysis, alcohol consumption was suggestive of an increased risk of adenocarcinoma but not of squamous cell carcinoma or other histologic types. The small number of case patients with lung cancer in this study limits our ability to make an inference about the association between alcohol intake and histologic types of lung cancer. There was no apparent dose–response relationship between alcohol consumption and histologic types of lung cancer, and the estimates were very unstable (wide 95% CIs, all of which included 1.0). We cannot provide a plausible explanation for the suggestive association between alcohol and adenocarcinoma, and chance cannot be excluded as a possible explanation for this association. In a recent case–control study by Zang and Wynder (21), no statistically significant association was observed between alcohol and squamous cell, adenocarcinoma, small-cell, or large-cell lung carcinoma. Furthermore, alcohol consumption was not associated with histologic type of lung cancer in another case–control study (27).

Our study has several strengths. We used stringent criteria to control confounding by cigarette smoking and other major risk

factors for lung cancer. Each case patient with lung cancer was matched to all potential control subjects on smoking status (never smoker, former smoker, or current smokers) and pack-years of smoking ( $\pm 2$  years), and former smokers were matched on years since quitting ( $\pm 2$  years). Information on alcohol consumption collected at several time points was used to evaluate exposure. The prospective nature of our study design, the long duration of follow-up, the completeness of case patient ascertainment, and the wide age range of participants are additional strengths. Nevertheless, our study has some limitations. We have a relatively small number of case patients with lung cancer to allow stratified analyses. Because 89% of our population consumed fewer than three alcoholic drinks per day, our results are limited primarily to light to moderate drinkers, and we could not evaluate the effects of heavy drinking on the risk of lung cancer. Finally, we may have underestimated alcohol consumption among former heavy drinkers who may have quit or reduced their alcohol intake before the initial alcohol assessment.

In conclusion, our data show that alcohol consumption that was generally light to moderate among subjects in the Framingham Study was not statistically significantly associated with the risk of lung cancer.

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## NOTES

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