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Prospective study of the association of alcohol with cancer of the upper aerodigestive tract and other sites

Ikuko Kato, Abraham M. Y. Nomura, Grant N. Stemmermann, and Po-Huang Chyou

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The association of alcohol consumption with cancers of the upper aerodigestive tract, hepato-biliary-pancreatic system, urogenital organs (except for prostate), and lymphohematopoietic tissue was evaluated in a prospective study of 6,701 American men of Japanese ancestry living in Hawaii. Compared with cancer-free subjects, subjects who subsequently developed cancers of the upper aerodigestive tract (oral-pharynx, esophagus, and larynx), liver, biliary tract, and lymphohematopoietic tissue consumed significantly larger amounts of total alcohol—mainly in the form of beer. Subjects who developed oral-pharyngeal and esophageal cancer also consumed larger amounts of wine and spirits. Because the upper aerodigestive tract cancers were associated positively with cigarette smoking, age-adjusted relative risks (RR) were calculated, based on joint exposure to cigarette smoking and heavy alcohol intake (⩾ 30 ml/day) in this population. A markedly increased risk was observed among subjects who were both heavy alcohol drinkers and smokers (RR = 17.3, 95 percent confidence interval [CI] = 6.7-44.2), compared with subjects who did not smoke and did not drink heavily. The risk for these cancers also was increased among heavy alcohol drinkers who were nonsmokers (RR = 8.6, CI = 2.1-36.0).

Key words: Alcohol, biliary tract, Hawaii, larynx, leukemia, liver, lymphoma, mouth, pharynx, United States.

Introduction

There is evidence that excessive alcohol intake increases the risk of liver cancer and upper-aerodigestive-tract cancer.[1-8] It also may increase the risk of breast and colorectal cancer.[6,9-12] In addition, a relation between alcohol and cancers of the stomach and pancreas has been suspected, but not confirmed.[1]

Although there is no consistent experimental evidence that ethanol is carcinogenic, various biochemical mechanisms have been proposed whereby alcohol consumption may promote carcinogenesis. These include the direct, tissue-toxic effects of acetaldehyde and superoxide metabolized from alcohol;[13] carcinogenic properties of nitrosamines and other contaminants detected in alcoholic beverages;[14] tumor-promoting effect of alcohol after the initiation of cancer;[15] alteration of hormonal balance;[16] an indirect effect through nutritional deficiencies associated with alcohol abuse;[17] and a co-carcinogenic effect by solubilizing a true carcinogen,[18] or by increased activation and decreased clearance of certain carcinogens in the liver.[19]

Dr Kato is currently with the Division of Epidemiology, Aichi Cancer Center Research Institute, Nagoya, Japan. Drs Nomura, Stemmermann, and Chyou are with the Japan-Hawaii Cancer Study, Kuakini Medical Center, Honolulu, HI. Address correspondence to Dr Nomura, Japan-Hawaii Cancer Study, Kuakini Medical Center, 347 N Kuakini St, Honolulu, HI 96817, USA. *This work was supported in part by Grant RO1 CA 33644 from the National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.*

Previous epidemiologic findings were based mainly on case-control and correlation studies. Case-control studies have potential methodologic problems in the selection of a suitable control group and in the possibility of recall bias. Other important epidemiologic findings on alcohol and cancer have been derived from cohort studies of presumed excessive drinkers (alcoholics and brewery workers) and populations known to have a low alcohol intake, such as Seventh-Day Adventists and Mormons.[1-3,5,6,9] The measurement of a dose-response effect is usually lacking in studies of excessive drinkers and it is difficult to assess the effect of heavy drinking in religion-based groups that proscribe alcohol intake. Prospective studies of general populations can overcome some of these limitations, but there has been a limited number of these studies on the relation between alcohol consumption and cancer, especially cancer incidence.

Our earlier prospective studies, based on a cohort of Japanese men living in Hawaii, revealed that alcohol consumption, especially beer, was associated positively with the risk of rectal cancer and that alcohol as a percentage of energy intake was associated positively with the risk of colon cancer.[10,11] There was no association with cancer of the stomach, lung, or prostate. In these studies, we also found a strong dose-response association of alcohol consumption with the risk of all other cancer sites combined (excluding cancer of the colon, rectum, stomach, lung, and prostate). We now report on the association of alcohol intake with the occurrence of cancer at several less common sites in the same cohort.

Material and methods

The subjects for this study were American men of Japanese ancestry, born from 1900 to 1919, and residing on the Hawaiian island of Oahu. They were identified by the Honolulu Heart Program in 1965 with the use of the comprehensive 1942 Selective Service draft registration files.[20] Of 11,148 men identified, 8,006 (71.8 percent) were interviewed and examined between 1965 and 1968. One hundred and eighty men (1.6 percent) died before they could be examined, and 2,962 (26.6 percent) declined participation in the program.

During the interview, information was collected on the following variables: cigarette smoking history, dietary history, and alcohol intake. In the diet history, a 24-hour diet-recall interview was administered to each subject using food models and serving utensils to estimate their total intake of calories, carbohydrates, fat, and protein.[21]

Two types of information on alcohol consumption were obtained: usual monthly intake (oz) of beer, spirits, and wine (including Japanese *sake*); and actual intake of each during the 24-hour period preceding the interview. For the purpose of this analysis, information on usual consumption during one month was used. Average monthly ethanol intake was estimated assuming that 1 oz of beer, wine, or spirits yielded 0.037, 0.10, or 0.38 oz of ethanol, respectively. Total ethanol intake was calculated by summing the ethanol content of beer, wine, and spirits. The unit of oz/month was converted to ml/day by multiplying by 29.6/30 (days). The measurement of alcohol consumption was carried out only during the single interview between 1965 and 1968. Any changes in the consumption of ethanol after 1968 were not included in this analysis.

Subsequent cases of cancer in the cohort have been identified through continuous surveillance of all general hospitals on Oahu, and through linkage with the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute. Each diagnosed case was confirmed by histologic examination. Based on a 19-year follow-up survey of the study subjects since their 1965-68 examination, it was determined that only 1.3 percent of the men could not be found on Oahu. As a result, the surveillance for incident cases of cancer should be nearly complete. The following subsets of subjects were excluded from analysis: 81 cancer cases diagnosed before examination; 137 suspected incident cases without histologic confirmation; 989 incident cases of cancers of the major sites previously studied (stomach, colon, rectum, lung, and prostate);[10,11] and 98 subjects without information on alcohol consumption. As a consequence, 6,701 subjects remained in the study.

The numbers of incident cases of cancers identified in the present study are as follows: 75 cases of upper aerodigestive tract cancer (oral-pharynx = 21, esophagus = 26, larynx = 24, other = 4); 89 cases of cancer of the hepato-biliary-pancreatic system (liver = 29, biliary tract = 24, pancreas = 36); 103 cases of cancer of the urogenital organs except for the prostate (uroepithelial = 83, renal cell = 19, other = 1); 72 cases of cancer of the lymphohematopoietic tissue (lymphoma = 36, leukemia = 31, other = 5); 85 cases of other miscellaneous sites of cancer (total of 20 sites). There were 6,277 cancer-free subjects.

Analysis of covariance[22,23] was used to calculate age-adjusted means of alcohol intake and other variables. Cox proportional hazards regression-models[24] were fitted to estimate covariate-adjusted relative risks (RR) and 95 percent confidence intervals (CI) for specific cancer according to levels of intake of alcohol. Three levels of alcohol intake were determined, so that suf-

ficient numbers of cases and noncases were included in each category. Covariates included: age at examination; current smoker status; age started smoking (current smokers); number of cigarettes smoked per day (current smokers); ex-smoker status; maximum number of cigarettes smoked per day (ex-smokers); and number of years this maximum amount was smoked (ex-smokers). This detailed history of cigarette smoking was included in the analysis to remove, as much as possible, the effects of smoking on cancer risk. To test for trend in risk, separate logistic regression models were fitted with a single alcohol variable, taking values of 1, 2, and 3 for the three levels of consumption (none, low, and high), respectively, while adjusting for the same covariates above. To evaluate beverage-specific effects, another Cox model was fitted with three continuous variables, each representing the amount of ethanol consumed in a specific type of beverage, and the aforementioned covariates. Each subject's time at risk was computed as the time from his examination to the diagnosis of cancer, death, or 30 March 1990, whichever occurred first. If more than one type of cancer was diagnosed in the same person, only the initially diagnosed cancer was considered.

Results

Table 1 shows the age-adjusted mean intake of total alcohol and the three different sources of alcohol (ml/day) among cancer cases (by specific site) and noncases. The monthly intake of total alcohol was more than three times higher in upper-aerodigestive-tract cancer cases than in noncases. The mean was the highest for oral-pharyngeal cancer, followed by cancers of the esophagus and larynx. The monthly intake of total alcohol was two times higher in cases of liver and biliary tract cancer than in noncases. Cases of cancers of the lymphohematopoietic tissue also had a higher mean intake of total alcohol compared with noncases.

Upper-aerodigestive-tract cancer cases consumed more of all types of alcoholic beverages, especially beer, compared with noncases. Wine (including Japanese *sake*) and spirits also were consumed more often by oral, pharyngeal, and esophageal cancer cases. A statistically significant difference ($P < 0.05$) between cases of cancers of the liver, biliary tract, and lymphohematopoietic tissue, and noncases was observed only for the consumption of beer.

When alcohol intake was measured as a percentage

Table 1. Comparison of age-adjusted mean intake (ml/day[a]) of total alcohol, beer, wine, and spirits, between cancer cases by site and noncases

Cancer site (ICD8 codes)	No.	Total alcohol		Beer		Wine		Spirits	
		Mean	P^b	Mean	P^b	Mean	P^b	Mean	P^b
Upper aerodigestive tract (140-150, 160-161)	75	39.3	<0.01	683.9	<0.01	35.6	<0.01	27.4	<0.01
Oral-pharynx (140-149)	21	44.7	<0.01	539.9	<0.01	95.7	<0.01	39.9	<0.01
Esophagus (150)	26	40.3	<0.01	681.1	<0.01	24.2	0.14	33.3	<0.01
Larynx (161)	24	38.4	<0.01	889.3	<0.01	1.9	0.58	14.0	0.38
Hepato-biliary-pancreatic system (155-157)	89	19.5	<0.01	372.3	<0.01	18.3	0.09	10.3	0.55
Liver (155)	29	25.9	<0.01	518.3	<0.01	14.4	0.54	13.6	0.37
Biliary (156)	24	22.7	0.04	441.4	0.04	23.2	0.18	10.8	0.70
Pancreas (157)	36	12.3	0.93	208.0	0.73	18.2	0.28	7.3	0.87
Urogenital organs (186-189)	103	15.2	0.28	274.8	0.42	10.3	0.69	10.5	0.48
Uroepithelial (188, 189.1, 189.2)	83	15.9	0.22	275.9	0.46	11.5	0.57	11.8	0.31
Renal cell (189.0)	19	13.0	0.94	287.4	0.64	4.6	0.79	5.1	0.68
Lymphohematopoietic tissue (200-207, 209)	72	19.9	<0.01	482.3	<0.01	3.8	0.52	8.4	0.97
Lymphoma (200-202)	36	20.9	0.04	501.5	<0.01	6.7	0.88	4.4	0.49
Leukemia (204-207)	31	21.6	0.04	432.6	0.02	2.4	0.57	14.1	0.32
Other miscellaneous sites	85	11.1	0.56	256.0	0.76	0.6	0.22	4.6	0.32
Noncases	6,277	12.6		236.2		8.1		8.2	

[a] ml/day refers to amount of ethanol in beverages for total alcohol and refers to the volume of the alcoholic beverages for beer, wine, and spirits.
[b] *P*-values for comparing each site-specific mean to that of noncases.

Table 2. Relative risks (RR) and 95% confidence intervals (CI) associated with total alcohol intake (ml/day), adjusted for age and cigarette smoking

Site of cancer		Total alcohol (ml/day)			Trend *P*
		0[a]	<30	≥30	
Oral-pharynx, esophagus larynx	No.	13	21	36	<0.01
	RR	1.0	1.2	5.4	
	CI	—	0.6-2.3	2.8-10.4	
Liver, biliary tract	No.	17	17	18	0.01
	RR	1.0	0.8	2.8	
	CI	—	0.4-1.5	1.4-5.6	
Leukemia, lymphoma	No.	19	25	21	<0.01
	RR	1.0	1.0	3.1	
	CI	—	0.6-1.9	1.6-5.9	
No. of noncases		2,341	2,992	889	

[a] Referent group.

Table 3. Relative risks (RR) and 95% confidence intervals (CI) associated with beer intake (ml/day), adjusted for age and cigarette smoking

Site of cancer		Beer intake (ml/day)			Trend *P*
		0[a]	<500	≥500	
Oral-pharynx, esophagus, larynx	No.	24	16	30	<0.01
	RR	1.0	0.7	2.6	
	CI	—	0.4-1.4	1.5-4.6	
Liver, biliary tract	No.	20	11	21	<0.01
	RR	1.0	0.6	2.9	
	CI	—	0.3-1.4	1.6-5.6	
Leukemia, lymphoma	No.	20	26	19	<0.01
	RR	1.0	1.5	2.8	
	CI	—	0.9-2.8	1.5-5.3	
No. of noncases		2,837	2,395	1,030	

[a] Referent group.

of total caloric intake based on the 24-hour dietary recall, the percentage was significantly higher than noncases only for cases of upper aerodigestive tract cancer. However, there were no significant differences in the age-adjusted mean intake of total calories, total fat, total protein, and total carbohydrate between each of the five case groups listed in Table 1 and the noncases (data not shown).

Relative risks (RR) according to different levels of total alcohol intake were calculated for three groups of cancer sites, with adjustment for age and cigarette smoking: cancers of the oral-pharynx; esophagus and larynx; cancers of the liver and biliary tract; and lymphoma and leukemia. Subjects without detailed smoking history were excluded from the analyses. As shown in Table 2, drinkers who consumed 30 ml or more of total alcohol per day had a statistically significant, greater risk for these cancer sites.

Table 4. Age-adjusted relative risks (RR) and 95% confidence intervals (CI) for cancer of the oral-pharynx, esophagus, and larynx associated with joint exposure to cigarette smoking and heavy alcohol drinking (≥30 ml/day)

Smoking status		Alcohol intake (ml/day)	
		<30	≥30
Never smokers	Cases/noncases	5/1,869	3/130
	RR	1.0[a]	8.6
	CI	—	2.1-36.0
Ex- and current smokers	Cases/noncases	29/3,508	34/769
	RR	3.3	17.3
	CI	1.3-8.4	6.7-44.2

[a] Referent group.

Because beer was the source of 69 percent of the total alcohol consumed by the study subjects, a similar analysis was made for beer intake for the same three groups of cancer sites. An increased risk for these sites of cancer also was observed in beer drinkers who consumed 500 ml or more per day (Table 3). The RR compared with subjects who did not drink beer was 2.6 for cancers of the oral-pharynx, esophagus, and larynx; 2.9 for cancers of the liver and biliary tract; and 2.8 for lymphoma and leukemia. When three continuous variables, each representing the amount of ethanol consumed in a specific type of beverage, were included in a Cox model to evaluate beverage-specific effects, the RR for alcohol from beer was significant for each of the three groups of cancer sites. In addition, the RRs for alcohol from wine and spirits were also statistically significant for cancers of the oral-pharynx, esophagus, and larynx combined.

Cancer of the upper-aerodigestive-tract was the only cancer site that was related significantly to cigarette smoking after adjustment for age and alcohol intake. Both past (RR = 2.7, 95 percent confidence interval [CI] = 1.2-6.1) and current smokers (RR = 3.6, CI = 1.7-7.6) had an increased risk. As a result, we calculated age-adjusted RRs for this group of cancer associated with joint exposure to cigarette smoking and relatively heavy alcohol-drinking (≥30 ml/day) among subjects with known smoking status (Table 4). When smokers (past and current) drank 30 oz or more of total alcohol per month, the RR was 17.3 compared with subjects who did not smoke and did not drink heavily. The exposure to relatively heavy alcohol-drinking *only* (RR = 8.6) or cigarette smoking *only* (RR = 3.3) also showed a significantly increased risk for this cancer site.

Discussion

The present study recorded information on individual quantitative estimates of total alcohol intake and the intake of several types of alcoholic beverage. Sixty-nine percent of the total alcohol consumed by this cohort came from beer, seven percent from wine, and 24 percent from spirits. These data were collected before the diagnosis of cancer was made. With detailed adjustment for cigarette smoking, the present study showed that relatively heavy alcohol-drinking was associated with an increased risk of cancer of the upper aerodigestive tract, liver, biliary tract, and lymphohematopoietic tissue.

An association between alcohol consumption and cancers of the upper aerodigestive tract has been observed consistently in cohort studies of alcoholics,[1-3] brewery workers,[5,6] male Japanese physicians,[4] participants in a multiphasic health examination program,[8] and in a large population group.[7] Precise information on individual drinking history also has been collected in a number of case-control studies,[25-30] almost all of which have demonstrated a dose-response relationship. The association was generally stronger for cancers of the pharynx, esophagus, and mouth, than for cancer of the larynx.[25-27] This suggests that local effect of alcohol is a major mode of increasing the risk of cancer at these sites.

Smoking[7,25-30] and malnutrition[19,28-30] have been associated with cancer risk at these sites and their synergistic effect with alcohol drinking has been reported.[7,19,25-27] Our study confirmed that joint exposure to smoking and heavy alcohol drinking markedly increases the risk of upper aerodigestive tract cancer.

Some cohort studies of alcoholics[1,3] and brewery workers[5,6] have shown an increased risk of death from liver cancer. The observed/expected ratio ranged from 1.5 to 2.0, although the association was not always statistically significant because of small numbers of cases. A cohort study of male Japanese physicians[4] and a follow-up study of HBsAg-positive blood donors[31] showed that the risk increased with increasing alcohol consumption. Several case-control studies have supported these results.[32-37] Although hepatitis B virus is a causative factor of liver cancer in this cohort, as we reported previously,[38] alcohol consumption also may promote hepatic damage.[39] There was no evidence of a synergistic effect with cigarette smoking and nutritional intake in relation to liver cancer risk in the present study.

Alcohol has been suspected to protect against the formation of gallstones, a major risk factor for biliary tract cancer, by altering cholesterol metabolism.[40-42] However, liver cirrhosis, which is associated with alcohol abuse, has been reported to increase the risk of gallstones.[43] Earlier reports have demonstrated neither an increased nor a decreased risk of biliary tract cancer associated with alcohol consumption. The findings on biliary tract cancer in the present study could be due to chance, but could also be explained on the basis of carcinogens excreted in the bile.[44]

Little attention has been paid to the association between alcohol consumption and hematopoietic malignancies. Although several cohort studies of presumed excessive drinkers showed only slightly negative association with these malignancies,[2,3,5] a significantly increased risk of leukemia was observed among Swedish brewery workers.[6] In a cohort study of Japanese subjects, the risk of leukemia was decreased among males who were daily drinkers but increased among females who were daily drinkers.[7] The Third National Cancer Survey study suggested a positive association between leukemia and alcohol consumption.[45] In a correlation study among five ethnic groups in Hawaii, there was a statistically significant, positive correlation between beer consumption and the incidence of leukemia.[46] It has been reported that alcohol has direct effects on erythrocyte and granulocyte precursors in the bone marrow, resulting in cellular vacuolization similar to that seen in chloramphenicol toxicity,[47] which has been associated with leukemia.[48] Impaired immune function among excessive drinkers[49] may contribute to an increased risk of lymphoma. It is generally accepted that persons of Asian descent have lower levels of alcohol dehydrogenase or acetylaldehyde dehydrogenase (or both) than their Caucasian counterparts.[50] This deficiency might be related to the increase in their susceptibility to lymphohematopoietic neoplasms.

Nitrosamines and other carcinogenic substances have been detected in several types of alcoholic beverages, including beer.[1,14] When studied by type of alcoholic beverages, only beer was related consistently to the increased risk of cancers of the upper aerodigestive tract, hepato-biliary system, and hematopoietic tissue in the present study. This was not surprising, in view of the fact that more than 60 percent of alcohol intake was attributable to beer in this population. Our study also showed that the subjects who developed oral, pharyngeal, or esophageal cancer consumed an excess of strong alcoholic beverages, *i.e.*, wine (including Japanese *sake*) and spirits. These alcoholic beverages may have exerted a stronger local effect on these cancer sites. Although several case-control studies also have found significant association with specific types of alcoholic beverages,[27-30] it is uncertain whether the type of alcoholic beverage or a greater con-

tribution to the total alcohol intake is more important in increasing cancer risk. Compared with other populations,[4,8,25-29] this Japanese population consumed lesser amounts of total alcohol. This would result in the relatively lower RR for drinkers compared with other studies. However, it is unlikely that the increased risks associated with relatively heavy alcohol-drinking are due to confounding factors. We eliminated the effects of cigarette smoking as much as possible and there were no differences in nutritional intake based on a 24-hour diet recall history between each case group and noncases.

Although some case-control studies have shown a possible relation between alcohol intake and pancreatic cancer,[51,52] the findings from past studies have been inconsistent.[53] The present study also did not support any association.

In conclusion, this prospective study among American men of Japanese ancestry in Hawaii confirmed the association between excessive alcohol drinking and increased risk of cancers of the upper aerodigestive tract and liver, and found that alcohol intake also may increase the risk of biliary tract cancer and hematopoietic malignancies. The latter findings require more attention in the future.

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