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ORIGINAL RESEARCH & CONTRIBUTIONS

Alcohol Intake, Beverage Choice, and Cancer: A Cohort Study in a Large Kaiser Permanente Population

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ABSTRACT

Context: Heavy intake of alcoholic beverages is associated with an increased risk of developing several types of cancers at specific body sites. However, evidence is conflicting regarding alcohol-associated cancers in other sites of the body as well as the role played by choice of wine, liquor, or beer.

Objective: To study incident cancer risk from 1978 to 1985 and through follow-up in 2012 relative to light-to-moderate and heavy drinking and to the choice of alcoholic beverage in a cohort of 124,193 persons.

Design: Cohort.

Main Outcome Measures: 1) Cox proportional hazards models controlled for 7 covariates to analyze alcohol-associated risk of any cancer and multiple specific types. 2) Similar analyses in strata of drinkers with or without a preponderant choice of wine, liquor, or beer and with or without inferred likelihood of underreporting.

Results: With lifelong abstainers as referent, heavy drinking (≥ 3 drinks per day) was associated with increased risk of 5 cancer types: upper airway/digestive tract, lung, female breast, colorectal, and melanoma, with light-to-moderate drinking related to all but lung cancer. No significantly increased risk was seen for 12 other cancer sites: stomach, pancreas, liver, brain, thyroid, kidney, bladder, prostate, ovary, uterine body, cervix, and hematologic system. For all cancers combined there was a progressive relationship with all levels of alcohol drinking. These associations were largely independent of smoking, but among light-to-moderate drinkers there was evidence of confounding by inferred underreporting. Beverage choice played no major independent role.

Conclusion: Heavy alcohol drinking is related to increased risk of some cancer types but not others. Because of probable confounding, the role of light-to-moderate drinking remains unclear.

INTRODUCTION

In observational studies[1-6] alcohol intake has been consistently associated with increased risk of cancers of the oral cavity, pharynx, larynx, esophagus, liver, large intestine, and female breast. Reports conflict about associations between alcohol consumption and risk of malignancies of the stomach, pancreas, lung, bladder, prostate, endometrium, ovary, cervix, and skin. Limited data suggest possible inverse (ie, protective) associations between alcohol consumption and the risk of renal cell carcinoma[7,8] and several types of hematologic malignancy.[9-11] It seems clear that a comprehensive study of the role of drinking in cancer risk should examine all cancer plus individual cancer types.

Although cancer risk is clearest for heavier intake of alcohol, some reports[1-5] suggest that light-moderate (light-to-moderate) drinking is also linked to increased cancer risk. Among specific cancer types, increased risk of light-moderate drinkers has most consistently been found in studies of female breast cancer.[12-14] The associations of lighter alcohol intake with cancer are relatively weak, and there are plausible confounders. Thus, the role of light-moderate drinking in cancer risk remains unresolved.

Because drinking and smoking are associated habits in many populations,[15,16] tobacco use is a potential confounder of some alcohol-cancer associations. Incomplete control for smoking could produce spurious alcohol associations with tobacco-related cancer types.[17] Underreporting of heavier intake is another possible source of spurious linkage of light-moderate drinking with increased risk of cancer.[18,19] Other potential confounders include chronic infections, diet, adiposity, exercise, air pollution, radiation exposure, and various chemicals.[17,19] However, most of these probably do not have sufficiently strong associations with drinking to explain the observed alcohol-cancer associations.

Independent roles for nonalcohol ingredients in alcoholic beverages have long been of interest. Early examples include reports of promotion of esophageal cancer by congeners in calvados (apple brandy)[20] and a possible role for beer in the risk of rectal cancer.[21] The latter was later considered confounded.[22] In recent years, interest about this aspect has focused on hypothetical protective effects of phenolic compounds in red wine, especially resveratrol.[23,24]

Hoping to cast light on several of these uncertainties, we have performed a cohort analysis in a large, multiethnic

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Northern California population. We report here data about risks for all cancer and specific cancer types associated with light-moderate and heavier drinking. The analysis is controlled for smoking and several other confounders. We also present data about risk of cancer among a strata of persons who drink preponderantly wine, liquor, or beer.

MATERIALS AND METHODS

Study Population and Data

The study protocols were approved by the Kaiser Permanente (KP) Northern California institutional review board. Baseline data were obtained from questionnaires given at health examinations from 1978 through 1985. The examinees were a multiethnic cohort of 124,193 men and women (mean baseline age = 41.0 years) who had no history of cancer and who were members of a comprehensive prepaid health plan in the San Francisco Bay Area. Usually taken as a voluntary routine health appraisal, the examination[25] included health measurements, self-classified ethnicity, and queries about sociodemographic status, habits, medical history, and symptoms. Data about alcohol consumption were supplied during the examination on a special check-sheet questionnaire. The study cohort comprised 79.8% of all examinees; the remainder included persons who took the examination during absences of a special research clerk and persons who declined, largely because of lack of fluency in English.

Lifelong abstainers were defined as persons who reported drinking no alcohol during the past year and "never or almost never" before the past year. Ex-drinkers were nondrinkers during the previous year who indicated prior alcohol drinking. Current drinkers described usual drinking as less than one drink per month ("special occasions only"), more than one drink per month but less than one drink per day, or as daily number of drinks, one to two, three to five, six to eight, and nine or more. Drinkers received separate questions about the number of days per week that they drank wine, liquor, or beer. Wine, liquor, or beer "preponderance" was defined among persons reporting more than one drink per month as exclusive intake of one beverage type or drinking the beverage type more days per week than either of the other two; preponderance was "none" for persons reporting more than one type with equal frequency.

Subjects with Cancer

Occurrence of cancer was ascertained from the KP Cancer Registry, which covers all subscribers and contributes to the local Surveillance, Epidemiology, and End Results (SEER) program. Codes were translated into International

Table 1. Selected traits of study cohort and cancer subjects[a]

Trait	Cohort, number (%)	Cancer, number (%)	Crude rate/1000 person-years
Total	124,193 (100)	18,637 (100)	8.4
Sex			
Men	55,040 (44.3)	8853 (47.5)	9.2
Women	69,153 (55.7)	9784 (52.5)	7.8
Race and ethnicity			
Black	33,625 (27.1)	5131 (27.5)	8.1
White	68,597 (55.2)	11,072 (59.4)	9.5
Asian	13,344 (10.7)	1522 (8.2)	5.9
Hispanic	5620 (4.5)	614 (3.3)	5.7
Other	2767 (2.2)	274(1.5)	5.7
Usual alcohol intake[b]			
Never	14,726 (11.9)	2065 (11.1)	7.6
Ex-drinker	3974 (3.2)	738 (4.0)	11.3
< 1 drink/day	71,805 (57.8)	9974 (53.5)	7.7
1-2 drinks/day	22,304 (18.0)	3807 (24.0)	9.7
≥ 3 drinks/day	10,051 (8.1)	1811 (9.7)	10.8
Alcoholic beverage preponderance[c]			
Wine	16,765 (13.5)	2672 (14.3)	8.9
Liquor	8696 (7.0)	1922 (10.3)	12.8
Beer	11,218 (9.0)	1361 (7.3)	7.2
None	41,267 (33.2)	5826 (31.2)	8.0
Smoking			
Never smoked	59,558 (48.0)	7656 (41.1)	6.98
Ex-smoker	27,501 (22.1)	5031 (27.0)	10.22
< 1 pack/day	20,762 (16.7)	3008 (16.1)	8.32
≥ 1 pack/day	11,351 (9.1)	2166 (11.6)	11.73
Unknown	5021 (4.0)	776 (4.2)	9.54
Body mass index			
< 25 kg/m^2	75,529 (60.8)	9699 (52.0)	7.30
25-29 kg/m^2	34,597 (27.9)	6378 (34.2)	10.09
≥ 30 kg/m^2	14,067 (11.3)	2560 (13.7)	10.01
Unknown	2319 (1.9)	302 (1.6)	7.84
Level of education			
No college	34,069 (27.4)	5979 (32.1)	9.88
Some college	42,480 (34.2)	6118 (32.8)	7.88
College graduate	44,899 (36.2)	6196 (33.3)	7.82
Unknown	2745 (2.2)	346 (1.9)	8.04

[a] Not all respondents answered all questions.
[b] There were also 1113 drinkers who did not state an amount of usual intake. These drinkers were included in a separate category in some models, but we present no data about these results.
[c] Among drinkers of > 1 per month (never drinkers, ex-drinkers, and drinkers of < 1 drink per month were excluded). Preponderant beverage drinkers reported more days per week consuming that beverage than either of the other 2 beverage types; if 2 or more types were reported with equal frequency, preponderance was "none."

Classification of Diseases, Ninth Revision (ICD-9) codes and the composite incidence of codes 140 to 209 (N = 18,637) was studied as "all cancer." Endpoints studied included any cancer and multiple specific cancer types. We report here data about the 15 types of cancer with 150 or more incident cases plus the following 3 composites: 1) Upper airway digestive (UAD) cancers included 552 subjects with 1 or more of codes 140 (lip), 141 (tongue), 143 (gum), 144 to 145 (mouth), 146 (oropharynx), 148 (hypopharynx), 149 (other oral cavity), 150 (esophagus), and 161 (larynx). 2) Hematologic malignancies included 1639 subjects with 1 or more of codes 201 (Hodgkin disease), 202 (non-Hodgkin lymphoma), 203 (multiple myeloma), 204 (lymphocytic leukemia), 205 (myelocytic leukemia), and 206 to 208 (other leukemia). 3) "Alcohol-related" malignancies included 9246 subjects with 1 or more of the following types: UAD, codes 153-154 (colorectal), 155 (liver), 162 (lung), 172 (melanoma), and 174 (breast). Table 1 presents selected distributions in the study population and subjects with cancer.

Analytic Methods

Subjects were followed until December 31, 2012, or until a diagnosis of cancer, their death, or other termination of Health Plan membership. The mean follow-up was 17.8 years, yielding an estimated 2,216,631 person-years of follow-up. Multivariate models used the Cox proportional hazards model. Alcohol was studied categorically. In most models, lifelong abstainers were the referent with 4 other categories: ex-drinkers, less than 1 drink per day (2 categories combined), 1 to 2 drinks per day, and 3 or more drinks per day (3 categories combined). Models for all persons and for subgroup strata included as covariates age (continuous), race or ethnicity (white referent, black, Asian, Hispanic, other), education (no college referent, some college, college graduate), body mass index (< 25 kg/m^2 referent, 25-29 kg/m^2, ≥ 30 kg/m^2), marital status (married referent, never married, formerly married), and cigarette smoking (never smoked referent, ex-smoker, current < 1 pack per day, current ≥ 1 pack per day).

Beverage choice was studied among persons reporting more than one drink per day. These drinkers were stratified into persons defined as reporting preponderance as wine, liquor, beer, or none. Models limited to each of these preponderance beverage groups ascertained the role of total alcohol in each stratum. These models used less than one drink per day in each preponderance as referent, plus one to two and three or more drinks per day as the other categories.

Among light-moderate drinkers, we studied strata of persons inferentially suspected or not suspected of underreporting alcohol intake. These strata were derived from subjects with at least two computer-stored examinations (index measurement and at least one other examination before or after). Suspected underreporters either reported heavier intake at another time or had an alcohol-related diagnosis (death certificate, hospitalization, or outpatient) at some time. A more detailed description of this method has been published.[9]

We report hazard ratios (HRs), 95% confidence intervals (CIs), and associated p values. The term *significant* is used in this article for p values < 0.05. We refer to persons reporting 3 or more drinks per day as "heavy" drinkers and to those reporting less than 1 or 1 to 2 drinks per day as "light-moderate" drinkers.

Table 2. Adjusted hazard ratios for all cancers by alcohol intake versus never drinkers in all subjects and selected groups[a]

Group	No. of cancer subjects	Alcohol intake			
		Ex-drinker (95% CI)	< 1 drink/day (95% CI)	1-2 drinks/day (95% CI)	≥ 3 drinks/day (95% CI)
All	18,637	1.2 (1.1-1.3)[b]	1.1 (1.1-1.2)[b]	1.2 (1.1-1.2)[b]	1.2 (1.2-1.3)[b]
Sex and race/ethnicity					
Men	8853	1.2 (1.1-1.4)[b]	1.1 (1.0-1.2)[c]	1.2 (1.1-1.4)[b]	1.2 (1.1-1.4)[b]
Women	9784	1.2 (1.0-1.3)[d]	1.1 (1.0-1.1)[d]	1.1 (1.0-1.2)[d]	1.3 (1.1-1.4)[b]
White	11,072	1.4 (1.2-1.5)[b]	1.2 (1.1-1.3)[b]	1.2 (1.1-1.4)	1.3 (1.2-1.5)[b]
Black	5131	1.1 (1.0-1.3)	1.0 (1.0-1.1)	1.1 (1.0-1.2)	1.2 (1.0-1.3)[d]
Asian	1552	1.0 (0.7-1.4)	1.1 (0.9-1.2)	1.3 (1.1-1.6)[c]	1.4 (1.0-1.8)[d]
Hispanic	614	1.2 (0.8-2.0)	0.8 (0.7-1.1)	0.9 (0.6-1.2)	1.2 (0.8-1.4)
Baseline smoking					
Never smoked	7656	1.2 (1.0-1.4)[d]	1.1 (1.0-1.2)[c]	1.2 (1.1-1.3)[b]	1.2 1.1-1.4)[c]
Ex-smoker	5031	1.3 (1.1-1.6)[c]	1.2 (1.0-1.3)[d]	1.2 (1.1-1.4)[c]	1.3 (1.1-1.5)[b]
Smoke < 1 pack/day	3008	1.1 (0.9-1.4)	0.9 (0.8-1.1)	1.0 (0.9-1.2)	1.1 (0.9-1.3)
Smoke ≥ 1 pack/day	2166	1.2 (0.9-1.6)	1.2 (0.8-1.7)	1.0 (0.8-1.2)	1.2 (0.9-1.5)
Interval between baseline examination and cancer diagnosis					
Cancer before 10 years	5185	1.4 (1.2-1.6)	1.2 (1.1-1.3)[b]	1.2 (1.1-1.4)[c]	1.4 (1.2-1.5)[b]
Cancer in 10-20 years	6295	1.3 (1.2-1.5)[b]	1.2 (1.1-1.3)[b]	1.3 (1.1-1.4)[b]	1.3 (1.2-1.5)[b]
Cancer after 20 years	7157	1.0 (0.9-1.2)	1.0 (1.0-1.2)	1.1 (1.0-1.2)[d]	1.2 (1.1-1.4)[c]

[a] Separate Cox proportional hazards models controlled for age, sex, race or ethnicity, body mass index, education, marital status, and smoking.
[b] p < 0.001.
[c] p < 0.01.
[d] p < 0.05.
CI = confidence interval.

RESULTS

All Cancer

The risk of any cancer was increased by 10% to 20% in daily drinkers (Table 2). The progressive nature of this relationship was partially masked by rounding; for example, for all persons the HR was 1.10 at less than 1 drink per day, 1.15 at 1 to 2 drinks per day, and 1.23 at 3 or more drinks per day. The magnitude of the increased risk was generally similar for the sexes, race/ethnic groups, and smoking strata but did appear to weaken after 20 years. Ex-drinkers also had a higher risk than lifelong abstainers, but not for cancers diagnosed after 20 years.

Specific Cancers

Table 3 presents data for specific cancer types and several composites. Heavy drinkers had a significantly increased risk of the following cancer types: UAD, colorectal, lung, melanoma, and breast. Light-moderate drinkers had an increased risk of all of these except lung cancer. The following types of cancer were unrelated to baseline alcohol intake: stomach, pancreas, liver, kidney, brain, thyroid, prostate, bladder, cervix, ovary, uterine body, and hematologic system. Ex-drinkers were at increased risk of UAD, liver, breast, and brain cancers. Table 3 includes data about the relationships of total alcohol intake to the alcohol-related composite; as expected, the HRs were larger than those for all cancer and were progressive with increasing alcohol intake.

Among UAD subgroups, heavier drinkers had an increased risk of each type. For example, for esophageal cancer the HR was 2.2 (CI = 1.0 to 4.9, $p < 0.05$), for laryngeal cancer it was 1.9 (CI = 1.2 to 3.0, $p < 0.01$) and for the remaining UAD cancers it was 2.6 (CI = 1.4 to 4.5, $p < 0.001$). The lower risk of heavy drinkers for hematologic malignancies was of borderline significance ($p = 0.06$). Among hematologic subtypes, all had inverse alcohol relationships, but p was < 0.05 only for lymphatic leukemia (HR = 0.5; CI = 0.3 to 0.98).

Alcohol-Associated Risk in Never Smokers

The data in Table 2 show generally similar alcohol-associated cancer risk among smoking strata, including never smokers. For the alcohol-related composite, the HR among never smokers reporting 3 or more drinks per day was 1.3 (CI = 1.1 to 1.6, $p < 0.001$). Three types of cancer had significant relationships among never smokers reporting 3 or more drinks per day, with these HRs: UAD = 1.3 (CI = 1.1 to 1.6), liver = 4.2 (CI = 2.2 to 2.8), and melanoma = 1.8 (CI = 1.2 to 2.8), all with $p < 0.001$.

Covariate Associations

Table 4 presents selected covariate data for all cancer and for the alcohol-related composite. For all cancer, age, male sex, black race, obesity, and smoking were associated with increased risk. For the composite, women had higher risk, driven by the large number with breast cancer, and black persons had slightly lower risk than whites, driven by the virtually total absence of melanoma. Smoking was slightly more strongly related to the composite, driven by the large number of lung cancer cases.

Beverage Preponderance Strata

With drinkers of less than 1 per day as referent, there was a significantly increased risk among heavy drinkers in the groups with a beer preponderance and with no beverage preponderance (Table 5); these findings were similar for men and women (data not shown). Analyses in the alcohol-associated composite showed that heavy drinkers in all preponderance groups evidenced significant associations, with a slightly larger HR for the beer preponderance group; these HRs were similar for men and women (data not shown) except for liquor preponderance (HR for men = 1.7, $p < 0.001$; for women, HR = 1.1, not significant). Relationships of heavy drinkers in preponderance groups differed for the individual cancers except that all groups showed significant associations with UAD; only beer was significantly associated with breast cancer; only wine was significantly related to melanoma. The no preponderance group had a significantly higher risk of liver cancer.

Suspected Underreporter Strata

Among light-moderate drinkers, increased alcohol-associated cancer risk was concentrated in the stratum suspected of underreporting. For example, among persons reporting 1 to 2 drinks per day on the index examination but

Table 3. Adjusted hazard ratios of alcohol intake versus never drinkers to incidence of specific cancers and selected composites[a]

Cancer type (ICD-9 code)	No. of cases	Ex-drinker (95% CI)	< 1 drink/day (95% CI)	1-2 drinks/day (95% CI)	≥ 3 drinks/day (95% CI)
Upper airway digestive[b]	552	2.9 (1.9-4.6)[c]	1.1 (0.8-1.6)	1.5 (1.1-2.3)[d]	2.5 (1.7-2.8)[c]
Stomach (151)	403	1.1 (0.7-1.8)	0.9 (0.7-1.2)	0.8 (0.6-1.4)	0.8 (0.5-1.3)
Colorectal (153-154)	2148	1.1 (0.9-1.4)	1.1 (1.0-1.3)	1.2 (1.0-1.4)[d]	1.4 (1.1-1.7)[e]
Liver (155)	213	1.9 (1.0-3.7)[d]	1.0 (0.6-1.5)	1.5 (0.9-2.5)	1.5 (0.8-2.7)
Pancreas (157)	535	1.3 (0.8-2.0)	0.9 (0.7-1.2)	1.1 (0.8-1.5)	1.0 (0.7-1.5)
Lung (162)	1989	1.2 (0.9-1.5)	1.0 (0.9-1.2)	1.0 (0.8-1.2)	1.3 (1.1-1.6)[e]
Melanoma (172)	1164	1.4 (0.9-2.2)	1.6 (1.2-2.1)[e]	1.9 (1.4-2.6)[c]	2.2 (1.6-3.1)[c]
Breast (174)	3639	1.3 (1.1-1.6)[d]	1.1 (1.0-1.2)[d]	1.2 (1.1-1.4)[e]	1.3 (1.1-1.5)[e]
Cervix (180)	727	1.2 (0.7-2.0)	1.0 (0.8-1.3)	1.0 (0.8-1.4)	1.0 (0.7-1.6)
Uterus (182)	689	0.7 (0.4-1.3)	1.0 (0.8-1.2)	1.0 (0.7-1.3)	1.1 (0.7-1.7)
Ovary (183)	341	1.2 (0.6-2.5)	1.2 (0.9-1.6)	1.2 (0.8-1.8)	1.2 (0.7-2.2)
Prostate (185)	3408	1.1 (0.9-1.3)	1.1 (0.9-1.2)	1.1 (1.0-1.3)	1.1 (1.0-1.4)
Bladder (188)	813	1.3 (0.9-2.0)	1.2 (0.9-2.6)	1.3 (0.9-1.7)	1.1 (0.8-1.6)
Kidney (189)	383	1.3 (0.8-1.2)	1.0 (0.7-1.4)	0.9 (0.6-1.4)	1.0 (0.6-1.6)
Brain (191)	186	2.7 (1.2-6.3)[d]	1.5(0.8-1.8)	1.5 (0.7-2.5)	1.4 (0.6-2.1)
Thyroid (193)	172	0.8 (0.3-2.3)	1.0 (0.6-1.6)	0.6 (0.3-1.1)	0.6 (0.3-1.4)
Hematologic (201-208)[f]	1639	0.8 (0.6-1.1)	1.1 (0.9-1.2)	1.0 (0.8-1.2)	0.8 (0.6-1.0)
Alcohol-related[g]	9246	1.4 (1.2-1.5)[c]	1.1 (1.0-1.2)[e]	1.2 (1.1-1.3)[c]	1.5 (1.3-1.6)[c]

[a] Separate Cox proportional hazards models controlled for age, sex, race or ethnicity, body mass index, education, marital status, and smoking.
[b] Includes ICD-9 codes 140 (lip), 141 (tongue), 143 (gum), 144-145 (mouth), 146 (oropharynx), 148 (hypopharynx), 149 (other oral cavity), 150 (esophagus), and 161 (larynx).
[c] $p < 0.001$.
[d] $p < 0.05$.
[e] $p < 0.01$.
[f] Includes codes 201 (Hodgkin disease), 202 (non-Hodgkin lymphoma, 203 (multiple myeloma), 204 (lymphocytic leukemia), 205 (myelocytic leukemia), and 206-208 (other leukemia).
[g] Includes upper airway digestive, liver, colorectal, lung, breast, and melanoma.
CI = confidence interval; ICD-9 = International Classification of Diseases, Ninth Revision.

considered likely underreporters, the HR for any cancer was 1.4 (CI = 1.3 to 1.7, p < 0.001), whereas among those considered unlikely to be underreporters, it was 1.1 (CI = 0.9 to 1.2). More details have been published.[19]

DISCUSSION

Disparate Alcohol-Cancer Relationships

Our analyses confirmed the presence of increased risk in drinkers for most of the cancer types consistently related to alcohol in prior reports. The exception was liver cancer, possibly because there were relatively small numbers of this type. Because never smokers, ex-drinkers, and heavy drinkers with a beer preponderance had an increased risk of liver cancer, we left this type of cancer in the alcohol-related composite. We also found that drinkers had an increased risk of lung cancer and of melanoma. We found no support for an alcohol association with stomach cancer, pancreatic cancer, or any type of genitourinary cancer in either sex. A slight inverse relationship with hematologic malignancies was of borderline significance. A weakening of this inverse association since our previous report[9] may be caused by a reduction in alcohol intake with increasing age. These disparities in alcohol-cancer associations are masked in the models for all cancer because the positive associations dominate.

Except for lung cancer, the increased cancer risk of baseline drinkers was present in both light-moderate drinkers and heavy drinkers, with progressive associations for all. The strongest alcohol-cancer associations among light-moderate drinkers were those with melanoma and breast cancer.

Table 4. Adjusted hazard ratios of selected covariates to risk of all and alcohol-related cancer[a]

Trait (referent)	Hazard ratio (95% CI)	
	All cancer, n = 18,637	Alcohol-related cancer, n = 9246
Age (× 10), years	1.7 (1.7-1.7)[b]	1.7 (1.6-1.7)[b]
Men (women)	1.2 (1.1-1.2)[b]	0.6 (0.6-0.6)[b]
Black (white)	1.1 (1.0-1.1)[c]	0.9 (0.9-1.0)[c]
Asian (white)	0.8 (0.8-0.9)	0.9 (0.8-0.9)[b]
Hispanic (white)	0.8 (0.7-0.9)[b]	0.7 (0.6-0.8)[b]
Body mass index > 30 kg/m^2 (< 25 kg/m^2)	1.1 (1.1-1.2)[b]	1.1 (1.0-1.1)[d]
Ex-smoker (never)	1.2 (1.1-1.3)[b]	1.2 (1.1-1.3)[b]
Smoke < 1 pack/day (never)	1.3 (1.3-1.4)[b]	1.5 (1.4-1.6)[b]
Smoke ≥ 1 pack/day (never)	1.8 (1.7-1.9)[b]	2.3 (2.1-2.4)[b]
College graduate (no college)	1.0 (1.0-1.1)	1.0 (1.0-1.1)
Never married (married)	1.0 (1.0-1.1)	0.9 (0.9-1.0)

[a] Cox proportional hazards models controlled for age, sex, race/ethnicity, body mass index, education, marital status, smoking, and alcohol intake. Please see text for definition of "alcohol-related cancer."
[b] p < 0.001.
[c] p < 0.01.
[d] p < 0.05.
CI = confidence interval.

Table 5. Adjusted hazard ratios of cancer by preponderant beverage type[a]

Group	Hazard ratio for ≥ 3 drinks per day vs < 1 per day (95% CI)			
	Wine, no. with cancer = 2671	Liquor, no. with cancer = 1922	Beer, no. with cancer = 1361	None, no. with cancer = 5826
All cancer	1.1 (1.0-1.3)	1.0 (0.9-1.2)	1.2 (1.0-1.3)[b]	1.2 (1.1-1.3)[b]
HbA_{1c}-related composite	1.3 (1.1-1.5)[b]	1.3 (1.1-1.6)[c]	1.5 (1.2-1.8)[c]	1.3 (1.1-1.4)[c]
UAD	2.1 (1.1-4.2)[d]	2.9 (1.5-5.5)[b]	2.9 (1.0-4.3)[d]	1.9 (1.3-2.8)[b]
Melanoma	1.7 (1.2-2.3)[b]	1.2 (0.7-2.1)	1.1 (0.6-2.0)	1.2 (0.8-1.6)
Breast	1.1 (0.8-1.5)	1.1 (0.8-1.6)	2.0 (1.1-3.4)[d]	1.1 (0.8-1.5)
Colorectal	1.4 (0.9-2.0)	1.4 (0.9-2.1)	1.6 (0.9-2.7)	1.4 (0.9-1.6)
Liver	1.0 (0.3-3.6)	0.4 (0.1-1.7)	2.0 (0.5-6.5)	2.3 (1.2-4.4)[d]
Lung	1.2 (0.8-1.7)	1.5 (1.0-2.1)[d]	1.5 (1.0-2.2)[d]	1.2 (1.0-1.5)

[a] Cox proportional hazards models controlled for age, sex, race/ethnicity, body mass index, education, marital status, smoking, and alcohol intake among drinkers of more than 1 drink per month (never drinkers, ex-drinkers, and drinkers of < 1 drink per month excluded). Preponderant beverage reported more days per week consuming that beverage than either of the other 2 beverage types; if 2 or more types were reported with equal frequency, preponderance was "none."
[b] p < 0.01.
[c] p < 0.001.
[d] p < 0.05.
CI = confidence interval; UAD = upper airway digestive; HbA_{1c} = HemoglobinA_{1c}.

Hypothetical Mechanisms

Although ethyl alcohol is not a mutagenic carcinogen, its first metabolite acetaldehyde probably is.[26,27] Hypothetically plausible mechanisms for alcohol-cancer associations vary with the sites. Genetic factors influencing alcohol metabolism may modulate alcohol-associated risk.[5,26,27] For UAD cancers it has been proposed that alcohol may operate as a promoter or facilitator of smoking-associated risk.[5,28] For UAD cancers, liver cancer, and breast cancer, a role has been proposed for acetaldehyde, which might damage DNA and thus act as a carcinogen.[26,27] Chronic liver disease, usually cirrhosis, is intermediary between heavy alcohol intake and hepatocellular cancer, analogous to the situation for chronic viral hepatitis and cancer.[26,27] There is evidence that an alcohol-estrogen interaction is involved in the breast cancer association.[12-14] Estrogenic hormones are an established risk factor for breast cancer, and several analyses, including ours,[14] show the increased breast cancer risk concentrated in women with estrogen-sensitive tumors. It has been suggested that relative folate deficiency may be involved in the relationships between alcohol and colorectal cancer, breast cancer, and others.[29] A more detailed discussion of these and other potential mechanisms is beyond the scope of this report.

Lung Cancer

The powerful relationship of smoking to lung cancer complicates the study of alcohol relations.[17,30,31] Published details of a KP analysis[17] show that the alcohol association primarily involved adenocarcinoma in heavy-drinking women. In that report the adenocarcinoma HR for 3 or more drinks per day among women was 2.1 (CI = 1.4 to 3.1, p = 0.0002), vs men with HR = 1.0 (CI = 0.7 to 1.5). The HR for squamous cell carcinoma among women reporting 3 or more drinks per day was 1.2 (CI = 0.7 to 2.0). The smoking-lung cancer association was stronger for squamous cell cancer than for adenocarcinoma, a fact lessening the likelihood that residual confounding by smoking was involved. We cannot explain the cell type specificity.

Melanoma

Although there are previous reports of a possible increased risk of melanoma in drinkers,[32] the association of drinking with an increased risk of melanoma in this analysis is noteworthy for its strength in both heavy and light drinkers. We have presented data showing that the alcohol-associated risk is similar for men and women.[33] In our data[34] and several other reports,[35] smoking is inversely related to melanoma, so residual confounding by smoking is not a plausible explanation for this finding. A noteworthy feature in our melanoma analyses is that the alcohol association is stronger for noninvasive than invasive disease,[34] suggesting an earlier diagnosis in drinkers. Earlier diagnosis could, in turn, be related to higher socioeconomic status and more recreational sun exposure. Among light-moderate drinkers wine preponderance is related to increased melanoma risk, another possible indicator of higher socioeconomic status.[36] We hope that further work by others will help to sort out the alcohol/smoking/melanoma puzzle.

Beverage Choice

Although the beverage type data suggest a slightly stronger association with beer than with wine or liquor, the differences were not large and the CIs overlapped. In this population, female heavy drinkers of beer have unfavorable lifestyle traits,[36] which may account for the slightly increased breast cancer risk in these women. We interpret our data as suggesting little, if any, disparity related to specific beverage types.

Limitations

As with all reported analyses of alcohol intake and cancer, this study is observational, leaving uncontrolled confounders (eg, dietary habits, cigar and pipe smoking, environmental smoke exposure, occupational factors, or exercise) as potential factors in the findings. Despite known relative stability of drinking in this population,[37] determination of alcohol habits only at baseline is another limitation. Changes in habits probably accounted for weakening alcohol associations with the passage of time.

The beverage choice data are limited by the fact that the primary queries about wine, liquor, and beer inquired about number of days per week rather than the usual number of drinks. Thus, we do not know the actual proportion of each person's intake represented. We do know from more detailed data in a 1984 to 1985 subset of examinees that there was good correlation of these values to the total number of drinks per week of the beverage type, with an average of 80% to 90% of alcoholic beverages consumed as the preponderant type.[36]

Public Health Consideration

Should these findings influence medical advice from health care professionals to patients? Increased cancer risk is clearly one of multiple medical reasons to avoid heavy drinking. The more important issue is the possible cancer risk of light-moderate alcohol intake. This issue remains clouded by uncertainty about whether the findings are confounded by underreporting and other traits. However, at present, a possible increased cancer risk at moderate intake should enter into individual estimations of the overall risk-benefit equation for alcohol drinking, especially for young persons. For most persons older than age 50 years, the overall benefits of lighter drinking, especially the reduced risk of atherothrombotic disease,[38,39] outweigh possible cancer risk. This is best evidenced by lower total mortality risk among middle-aged and older light-moderate drinkers.[39] For younger persons, especially young women with no coronary disease risk factors, the breast cancer data suggest the wisdom of limiting alcohol intake to very modest amounts. As always in medical practice, advice needs to be individualized.[40] ❖

We interpret our data as suggesting little, if any, disparity related to specific beverage types.

Disclosure Statement

All authors have participated actively in the execution of the study and/or preparation of the manuscript. The authors(s) have no conflicts of interest to disclose.

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Vital and Animal Spirits

After a man has taken wine or other spirituous liquors he is at once revived and restored. The reason is that in the mouth, oesophagus and stomach there are certain vital and animal spirits constantly scattered, roaming and, as it were, keeping watch. [Because these spirits are] analogous and proportionate to (those) in wine … they readily mix. Then, taking their new guests by the hand, as it were, convey them to the heart and brain.

— Thomas Willis, 1621-1675, English physician contributor to the disciplines of anatomy, neurology, and psychiatry; founding member of the Royal Society