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Original Contribution

Prospective Study of Alcohol Consumption Quantity and Frequency and Cancer-Specific Mortality in the US Population

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Prospective associations between quantity and frequency of alcohol consumption and cancer-specific mortality were studied using a nationally representative sample with pooled data from the 1988, 1990, 1991, and 1997–2004 administrations of the National Health Interview Survey ($n = 323{,}354$). By 2006, 8,362 participants had died of cancer. Cox proportional hazards regression was used to estimate relative risks. Among current alcohol drinkers, for all-site cancer mortality, higher-quantity drinking (≥3 drinks on drinking days vs. 1 drink on drinking days) was associated with increased risk among men (relative risk (RR) = 1.24, 95% confidence interval (CI): 1.09, 1.41; *P* for linear trend = 0.001); higher-frequency drinking (≥3 days/week vs. <1 day/week) was associated with increased risk among women (RR = 1.32, 95% CI: 1.13, 1.55; *P*-trend < 0.001). Lung cancer mortality results were similar, but among never smokers, results were null. For colorectal cancer mortality, higher-quantity drinking was associated with increased risk among women (RR = 1.93, 95% CI: 1.17, 3.18; *P*-trend = 0.03). Higher-frequency drinking was associated with increased risk of prostate cancer (RR = 1.55, 95% CI: 1.01, 2.38; *P* for quadratic effect = 0.03) and tended to be associated with increased risk of breast cancer (RR = 1.44, 95% CI: 0.96, 2.17; *P*-trend = 0.06). Epidemiologic studies of alcohol and cancer mortality should consider the independent effects of quantity and frequency.

alcohol drinking; cohort studies; diet; food habits; mortality; neoplasms; risk factors

Abbreviations: ICD, *International Classification of Diseases*; NHIS, National Health Interview Survey.

Little is known about associations between the quantity and frequency of alcohol consumption and all-site and cancer-specific mortality. Epidemiologic studies have typically examined total alcohol consumption (1), a measure that combines quantity and frequency, effectively obscuring their independent effects. Furthermore, studies of quantity and frequency (2–7) have focused more on cancer incidence (3–7) than cancer mortality (2, 3).

We previously performed a study of alcohol quantity and frequency and all-site cancer mortality (2) using nationally representative data from the 1988 National Health Interview Survey (NHIS). In that study, higher-quantity drinking was associated with increased risk of all-site cancer mortality in men, higher-frequency drinking was associated with increased risk in both genders, and quantity-frequency effects were masked by total alcohol consumption. Cancer-specific analyses were not performed because of an insufficient sample size; the study was limited to a single NHIS year with follow-up through 2002 only. Other studies found that infrequent heavy drinking was associated with increased prostate cancer incidence (3), that higher-frequency drinking was inconsistently associated with breast cancer incidence (4–6), and that higher-quantity drinking was associated with increased breast cancer incidence (7).

Our purpose in the current study was to examine associations between alcohol quantity and frequency and cancer mortality from all sites and the lung, colorectum, prostate, and breast, using a nationally representative sample with pooled data from the 1988, 1990, 1991, and 1997–2004 administrations of the NHIS, with follow-up through 2006.

MATERIALS AND METHODS

Study population and design

The NHIS, conducted by the National Center for Health Statistics, is a continuing annual, cross-sectional, nationally representative probability survey of household civilian, noninstitutionalized residents of the contiguous United States (8). The NHIS uses a multistage probability sampling design and oversamples black and Hispanic individuals. Door-to-door, in-home interviews are conducted by Census Bureau interviewers. The confidentiality of responses is assured by the federal Public Health Service Act.

In our study, we pooled data from 11 NHIS years in which information on the quantity and frequency of alcohol consumption was collected: 1988, 1990, 1991, and 1997–2004. Participants were ≥18 years of age, except in 1991 (for 1991, alcohol data were available only for participants aged 18–44 years). Response rates ranged from 69.6% (1999) to 86% (1988). Participants were followed for vital status and cancer-specific mortality through December 31, 2006, using National Center for Health Statistics public data sets linking each year of NHIS data to the National Death Index.

Alcohol consumption

Lifetime alcohol drinking status was assessed. Participants who had not consumed alcohol in the past year were categorized as never drinkers (if they had also consumed fewer than 12 drinks over the course of their lifetime), lifetime infrequent drinkers (if they had consumed 12 or more drinks in their lifetime but fewer than 12 drinks in any previous year), or former drinkers (if they had consumed 12 or more drinks in their lifetime and 12 or more drinks in any previous year but no drinks in the past year). Participants who had consumed 1 or more drinks in the past year (12 or more drinks in the past year for 1988) were categorized as current drinkers; in 1990, the reporting period was the past 2 weeks, with a query asking whether these 2 weeks were typical of the past year.

For current drinkers, data were available on usual alcohol quantity (number of drinks consumed, on average, on drinking days) and frequency (average number of drinking days per week). Usual quantity was classified as 1, 2, or ≥3 drinks per day and usual frequency as <1, 1–2, or ≥3 days per week. Total alcohol consumption (quantity multiplied by frequency (average number of drinks per week)) was characterized as light, moderate, or heavier. In women, light drinking was defined as ≤3 drinks per week, moderate drinking as >3–7 drinks per week, and heavier drinking as >7 drinks per week; in men, the corresponding ranges were ≤3 drinks per week, >3–14 drinks per week, and >14 drinks per week.

Covariates

We included covariates on which data had been collected in a similar manner in each of the pooled NHIS survey years. These variables included race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), education (less than high school/other, high school, or more than high school), region (Northeast, South, Midwest, or West), marital status (married vs. not married/other), smoking status (never, former, or current smoker; among current smokers, tertiles of smoking intensity were defined by the usual number of cigarettes smoked per day), and body mass index. Body mass index (calculated as weight (in pounds) × 704.54686/height (in inches) squared) was categorized as underweight (<18), normal weight (18–24.9), overweight (25–29.9), or obese (≥30). General health status (excellent, very good, good, or fair/poor/unknown) was considered in sensitivity analyses.

Analytic cohort

Of 364,366 participants asked about their alcohol consumption, we excluded 16,833 with insufficient information from NHIS–National Death Index data linkage, 2,420 who had a missing birth date or died within the quarter of their survey interview year, and 3,465 with missing data on drinking status; this left 341,648 participants (146,861 men and 194,787 women). Of those, 188,077 participants (97,762 men and 90,315 women) were current drinkers. Among the current drinkers, 14,710 participants (7,000 men and 7,710 women) were excluded because they did not report both quantity and frequency or because they were among the 5,996 participants from the 1990 NHIS whose past-2-week alcohol intake was not typical of the past year. We further excluded 3,584 respondents from the 1991 NHIS because it was not possible to determine whether they were former drinkers or lifetime infrequent drinkers. Therefore, our analytic cohort included 323,354 participants.

Mortality

Deaths occurring between baseline (1988 NHIS interview quarter) and December 31, 2006, were coded for the underlying cause using National Center for Health Statistics bridge codes spanning the Ninth (ICD-9) and Tenth (ICD-10) revisions of the *International Classification of Diseases* (ICD-9, 1979–1998; ICD-10, 1999–present) (9). Deaths from cancer at all sites and deaths from lung, colorectal, prostate, and breast cancer were coded using bridge codes 19–44, 27, 23, 33, and 29, respectively. To determine all-site cancer mortality, participants were followed until their date of death or December 31, 2006 (end of follow-up), whichever came first. For determination of cancer-specific mortality, the procedure was similar except that deaths due to causes other than the one of interest and that occurred before the end of follow-up were censored at the date of death.

Statistical analysis

To determine whether data could be pooled across survey years, adjusted associations between total alcohol consumption and all-site cancer mortality were examined by survey year (except for 1991, excluded because of a small sample size) using methods described below. Pooling was supported by the existence of similar associations across years.

First, we examined baseline associations between alcohol consumption and covariates using Wald F tests that accounted for the complex sample design of the NHIS for categorical and continuous variables (10). Second, we examined

Table 1. Weighted Baseline Characteristics of a Pooled National Health Interview Survey Cohort (1988, 1990, 1991, and 1997–2004; $n = 323,354$), by Total Alcohol Consumption, United States[a]

Baseline Characteristic	Men ($n = 138,590$)					
	Alcohol Drinking Status			Drinking Level (Among Current Drinkers)		
	Never Drinker	Former Drinker	Lifetime Infrequent Drinker	Light	Moderate	Heavier
No. of participants	18,808	14,475	14,545	47,964	33,084	9,714
Person-years of follow-up	139,825	126,027	102,124	398,195	293,271	87,951
Mean age, years	42.3 (0.2)[b]	54.0 (0.2)	49.6 (0.2)	41.7 (0.1)	42.5 (0.1)	41.4 (0.2)
Race/ethnicity, %						
Non-Hispanic white	61.5	79.5	71.6	76.4	80.6	79.7
Non-Hispanic black	16.1	10.3	13.5	8.6	7.9	8.6
Hispanic	14.3	7.7	10.0	11.0	9.1	9.2
Other	8.1	2.5	5.0	4.0	2.5	2.5
Education, %						
Less than high school/other	23.8	27.5	21.1	12.1	11.9	19.6
High school	33.9	34.4	34.3	30.1	30.9	38.2
More than high school	42.2	38.0	44.6	57.8	57.3	42.3
Region, %						
Northeast	14.9	16.5	17.7	20.6	21.2	17.3
Midwest	20.3	24.9	23.9	26.2	26.6	26.4
South	45.2	38.9	40.9	33.1	31.7	36.1
West	19.5	19.7	17.5	20.1	20.6	20.2
Marital status, %						
Married	56.0	71.2	69.8	64.7	59.7	50.1
Not married/other	44.0	28.8	30.2	35.3	40.3	49.9
Smoking status, %						
Never smoker	76.1	27.4	48.6	49.5	38.2	23.4
Former smoker	12.2	48.2	29.0	25.8	28.6	23.2
Current smoker[c]						
First tertile	3.5	4.6	4.8	7.2	9.6	10.5
Second tertile	3.4	6.9	6.0	7.4	10.3	14.1
Third tertile	4.8	12.9	11.5	10.1	13.2	28.8
Body mass index[d], %						
Underweight (<18)	0.8	0.6	0.4	0.4	0.3	0.7
Normal weight (18–24.9)	36.4	31.7	29.7	32.7	35.5	38.1
Overweight (25–29.9)	36.6	41.6	40.8	42.6	44.8	41.2
Obese (≥30)	17.2	21.2	22.2	19.4	15.8	16.6
Missing data	9.0	4.9	6.8	4.9	3.6	3.5

Table continues

associations between total alcohol consumption and cancer mortality with current drinking categorized as light, moderate, or heavier (referent group: never drinkers). Finally, among current drinkers, we examined associations between quantity (referent group: lowest quantity) and frequency (referent group: lowest frequency), which were mutually adjusted, and cancer mortality.

Cox proportional hazards regression models were used to compute relative risks of all-site and cancer-specific mortality using age as the time line (11). Cox model results were adjusted for race/ethnicity, education, region, marital status, smoking status (including tertiles of smoking intensity among current smokers), and body mass index, as well as gender (as appropriate).

For lung cancer, we also tested the interaction between drinking and smoking for both total alcohol consumption and quantity and frequency in models containing covariates; none of the interactions was statistically significant. Further,

Table 1. Continued

Baseline Characteristic	Women (n = 184,764)					
	Alcohol Drinking Status			Drinking Level (Among Current Drinkers)		
	Never Drinker	Former Drinker	Lifetime Infrequent Drinker	Light	Moderate	Heavier
No. of participants	53,931	13,738	34,490	62,009	12,962	7,634
Person-years of follow-up	423,124	139,790	276,893	541,710	117,628	69,934
Mean age, years	48.2 (0.2)	50.2 (0.2)	48.9 (0.1)	41.3 (0.1)	44.2 (0.2)	43.3 (0.3)
Race/ethnicity, %						
Non-Hispanic white	59.8	80.5	74.6	81.3	86.8	85.8
Non-Hispanic black	17.2	10.9	13.1	8.5	6.9	7.9
Hispanic	16.2	6.5	9.1	7.6	4.8	4.7
Other	6.8	2.2	3.2	2.6	1.6	1.7
Education, %						
Less than high school/other	28.4	21.2	18.4	8.6	7.3	10.6
High school	36.4	37.5	38.1	30.9	29.3	31.8
More than high school	35.2	41.3	43.5	60.5	63.4	57.5
Region, %						
Northeast	15.2	18.9	20.7	22.3	23.3	19.6
Midwest	19.2	26.4	26.5	28.0	26.1	25.4
South	46.8	34.7	35.6	30.4	29.0	32.4
West	18.8	20.0	17.3	19.3	21.6	22.6
Marital status, %						
Married	53.5	58.6	59.6	59.3	57.0	50.8
Not married/other	46.5	41.4	40.4	40.7	43.0	49.2
Smoking status, %						
Never smoker	82.2	41.3	59.3	53.2	41.4	26.8
Former smoker	8.1	33.9	19.3	21.7	27.0	25.1
Current smoker[c]						
First tertile	3.3	6.5	5.9	8.4	11.3	13.4
Second tertile	3.1	9.0	7.0	9.0	11.1	16.1
Third tertile	3.4	9.4	8.5	7.6	9.3	18.7
Body mass index[d], %						
Underweight (<18)	2.9	2.8	2.1	2.8	3.2	3.6
Normal weight (18–24.9)	40.7	41.1	38.9	50.8	59.4	57.4
Overweight (25–29.9)	26.7	26.1	27.2	23.9	22.0	23.2
Obese (≥30)	19.9	21.9	22.6	15.6	9.8	10.3
Missing data	9.7	8.2	9.2	6.8	5.7	5.4

[a] All P values were less than 0.001 for chi-squared tests of drinking status and drinking level by race/ethnicity, education, region, marital status, smoking status, and body mass index. All P values were less than 0.001 for adjusted Wald F tests of drinking status and drinking level with respect to age.
[b] Numbers in parentheses, standard error.
[c] Tertiles represent the distribution of smoking intensities among current smokers.
[d] Body mass index was calculated as weight (in pounds) × 704.54686/height (in inches) squared.

because lung cancer is strongly associated with smoking and smoking is related to drinking, we repeated the lung cancer analyses among participants who had never smoked cigarettes in order to account as thoroughly as possible for residual confounding.

The significance of linear trends and quadratic effects across drinking categories was determined using sample weighted median values within alcohol categories as continuous independent variables and t tests of the resulting regression coefficients. The proportional hazards assumption was

Table 2. Adjusted Relative Risks of All-Site and Cancer-Specific Mortality, by Total Alcohol Consumption, in a Pooled National Health Interview Survey Cohort, United States, 1988–2006[a,b]

Cancer Site and Drinking Status[c]	All Participants (n = 323,354)			Men (n = 138,590)			Women (n = 184,764)		
	No. of Deaths	RR	95% CI	No. of Deaths	RR	95% CI	No. of Deaths	RR	95% CI
All-site cancer									
Never drinker (referent)	1,958	1		460	1		1,498	1	
Former drinker	1,572	1.15	1.05, 1.25	950	1.25	1.09, 1.45	622	1.05	0.94, 1.17
Lifetime infrequent drinker	1,450	0.97	0.90, 1.06	493	1.04	0.90, 1.21	957	0.92	0.84, 1.01
Current drinker									
Light	1,669	0.87	0.80, 0.94	874	1.00	0.87, 1.15	795	0.75	0.68, 0.84
Moderate	1,091	0.96	0.87, 1.06	804	1.07	0.93, 1.23	287	0.91	0.77, 1.06
Heavier	622	1.27	1.14, 1.43	377	1.41	1.19, 1.67	245	1.20	1.02, 1.41
P-trend[d]		<0.001			<0.001			<0.001	
Lung cancer									
Never drinker (referent)	389	1		131	1		258	1	
Former drinker	556	1.17	1.00, 1.37	345	1.14	0.90, 1.45	211	1.14	0.92, 1.42
Lifetime infrequent drinker	396	0.97	0.82, 1.13	150	0.88	0.68, 1.13	246	0.99	0.81, 1.22
Current drinker									
Light	449	0.79	0.67, 0.92	253	0.81	0.64, 1.02	196	0.70	0.56, 0.89
Moderate	350	0.85	0.72, 1.01	259	0.85	0.67, 1.07	91	0.83	0.61, 1.12
Heavier	260	1.30	1.07, 1.56	161	1.21	0.93, 1.57	99	1.37	1.04, 1.80
P-trend		<0.001			0.003			<0.001	
Lung cancer (never smokers only)									
Never drinker (referent)	121	1		33	1		88	1	
Former drinker	33	1.15	0.69, 1.91	17	0.90	0.45, 1.79	16	1.31	0.73, 2.33
Lifetime infrequent drinker	51	1.01	0.68, 1.50	20	1.01	0.54, 1.89	31	0.97	0.59, 1.60
Current drinker									
Light	34	0.59	0.38, 0.92	15	0.47	0.26, 0.82	19	0.67	0.35, 1.28
Moderate	23	0.93	0.51, 1.71	13	0.52	0.25, 1.08	10	2.03	0.92, 4.46
Heavier	6	0.96	0.38, 2.48	3	0.52	0.14, 1.92	3	1.48	0.41, 5.30
P-trend		0.74			0.31			0.06	

Table continues

tested for levels of total alcohol consumption by comparing the relative risks for drinking categories in 6 gender-specific age groups: <65 years, 65–79 years, and ≥80 years. The proportional hazards assumption was met for each of the cancers studied (lung, colorectal, prostate, and breast) but not for cancer at all sites (see Web Table 1 (http://aje.oxfordjournals.org/) for all-site cancer results by gender-specific age group).

A series of sensitivity analyses was performed based on total alcohol consumption to determine whether our results were robust. Models separately 1) excluded participants who died within 2 years of their baseline interview (to reduce the impact of preclinical disease); 2) excluded participants who reported ever having cancer other than skin cancer (1997–2004) or lung cancer (1988) (to reduce the impact of preexisting disease); 3) restricted follow-up of each survey to 10 years (to reduce misclassification over longer periods of follow-up); 4) excluded participants younger than age 40 years at baseline (due to low risk of cancer mortality); 5) stratified baseline hazards according to 5- and 10-year birth cohorts; 6) included general health status as a covariate; 7) included binge drinking (yes, no) as a covariate (for all years except 1990—variable not available); and 8) included survey year as a covariate. Results from the sensitivity analyses were generally similar to those reported here.

Analyses were performed using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina) and SUDAAN, version 10 (Research Triangle Institute, Research Triangle Park, North Carolina); the latter is a statistical software package that takes into account the complex sampling design of the NHIS, permitting survey-design-based estimation of relative risks and their standard errors and tests of hypotheses. All analyses were weighted to the US population. All tests of significance were 2-tailed, with the level of significance set at $P < 0.05$.

Table 2. Continued

Cancer Site and Drinking Status[c]	All Participants (n = 323,354)			Men (n = 138,590)			Women (n = 184,764)		
	No. of Deaths	RR	95% CI	No. of Deaths	RR	95% CI	No. of Deaths	RR	95% CI
Colorectal cancer									
Never drinker (referent)	229	1		41	1		188	1	
Former drinker	152	1.25	0.97, 1.60	90	1.48	0.95, 2.30	62	1.08	0.76, 1.52
Lifetime infrequent drinker	162	1.06	0.86, 1.32	52	1.24	0.77, 1.98	110	0.98	0.76, 1.27
Current drinker									
Light	163	0.86	0.67, 1.10	84	1.05	0.66, 1.67	79	0.74	0.53, 1.03
Moderate	102	1.04	0.78, 1.39	75	1.22	0.78, 1.91	27	0.99	0.59, 1.68
Heavier	42	1.01	0.70, 1.47	25	1.08	0.60, 1.96	17	1.05	0.61, 1.80
P-trend		0.24			0.40			0.33	
Prostate cancer (men) or breast cancer (women)									
Never drinker (referent)				83	1		228	1	
Former drinker				111	1.12	0.81, 1.55	98	1.26	0.93, 1.70
Lifetime infrequent drinker				54	1.00	0.67, 1.48	146	0.90	0.70, 1.17
Current drinker									
Light				83	0.93	0.66, 1.30	128	0.75	0.57, 0.98
Moderate				85	1.22	0.86, 1.72	46	1.02	0.66, 1.57
Heavier				22	0.89	0.51, 1.56	31	1.09	0.68, 1.76
P-trend					0.70			0.43	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Pooled data from the 1988, 1990, 1991, and 1997–2004 administrations of the National Health Interview Survey, with follow-up through 2006.

[b] Relative risks were adjusted for race/ethnicity, education, region, marital status, smoking status (including tertiles of smoking intensity among current smokers), and body mass index, as well as gender (as appropriate).

[c] For definitions of quantity and frequency, see Materials and Methods.

[d] *P* for linear trend based on the adjusted Wald *F* test; lifetime infrequent drinkers and former drinkers were excluded.

RESULTS

Among the 323,354 participants and 2,716,472 person-years of follow-up, there were 8,362 deaths from all cancers (excluding nonmelanoma skin cancer), including 2,400 deaths from lung cancer (268 of these among never smokers), 850 from colorectal cancer, 438 from prostate cancer, and 677 from female breast cancer.

Former drinkers tended to be older than never drinkers (Table 1) and were more likely to be white. Among current drinkers, heavier drinkers were more likely to smoke and to smoke heavily. Heavier drinkers also had less education.

In the analyses described below, results were adjusted for race/ethnicity, education, region, marital status, smoking status (including tertiles of smoking intensity among current smokers), and body mass index, as well as gender (as appropriate); in analyses of quantity and frequency among current drinkers, results were mutually adjusted (i.e., quantity was adjusted for frequency and vice versa). For analyses of total alcohol consumption, the referent group was never drinkers. For analyses of quantity and frequency, which were conducted only among current drinkers, the referent groups were the lowest levels of each.

Total alcohol consumption

Among all participants, former drinkers had a significant 15% increased risk of all-site cancer mortality in comparison with never drinkers; this higher risk was driven primarily by a significant 25% increased risk among male former drinkers (Table 2). However, former drinkers were not at significantly increased risk in cancer-specific analyses of lung, colorectal, prostate, and breast cancer. Lifetime infrequent drinkers were not at increased risk of either all-site cancer mortality or cancer-specific mortality.

Current drinkers who drank most heavily, in comparison with never drinkers, had the greatest risk of all-site cancer mortality, with significantly increased risks of 27% among all participants, 41% among men, and 20% among women; in addition, among women, light drinking tended to be protective, with a risk reduction of 25% (quadratic effect: $P = 0.06$). Current drinkers who drank most heavily also had the greatest risk of lung cancer mortality, with significantly increased risks of 30% among all participants and 37% among women. In addition, light drinking was protective among all participants (quadratic effect: $P = 0.03$), with a 21% risk reduction, and among women (quadratic effect: $P = 0.05$), with a 30%

Table 3. Adjusted Relative Risks of All-Site and Cancer-Specific Mortality, by Alcohol Quantity and Frequency Among Current Drinkers ($n = 173{,}367$), in a Pooled National Health Interview Survey Cohort, United States, 1988–2006[a,b]

Cancer Site and Drinking Pattern[c]	All Participants				Men				Women			
	No. of Deaths	Total No. of Persons	RR	95% CI	No. of Deaths	Total No. of Persons	RR	95% CI	No. of Deaths	Total No. of Persons	RR	95% CI
All-site cancer												
$Q = 1$ (referent)	1,333	54,986	1		686	22,352	1		647	32,634	1	
$Q = 2$	1,034	56,651	1.08	0.98, 1.19	610	28,143	1.06	0.92, 1.21	424	28,508	1.12	0.97, 1.29
$Q \geq 3$	1,015	61,730	1.22	1.10, 1.36	759	40,267	1.24	1.09, 1.41	256	21,463	1.18	0.99, 1.41
P-trend[d]			<0.001				0.001				0.06	
$F < 1$ (referent)	985	72,109	1		486	29,633	1		499	42,476	1	
$F = 1$–2	991	63,473	0.94	0.85, 1.05	617	36,028	0.93	0.82, 1.07	374	27,445	0.96	0.82, 1.12
$F \geq 3$	1,406	37,785	1.14	1.03, 1.25	952	25,101	1.06	0.94, 1.20	454	12,684	1.32	1.13, 1.55
P-trend			<0.001				0.08				<0.001	
Lung cancer												
$Q = 1$ (referent)	331	54,986		1	174	22,352	1		157	32,634	1	
$Q = 2$	341	56,651	1.28	1.08, 1.53	201	28,143	1.25	0.98, 1.58	140	28,508	1.36	1.05, 1.76
$Q \geq 3$	387	61,730	1.44	1.20, 1.72	298	40,267	1.48	1.18, 1.85	89	21,463	1.28	0.93, 1.77
P-trend			0.001				0.002				0.09	
$F < 1$ (referent)	282	72,109		1	152	29,633	1		130	42,476	1	
$F = 1$–2	277	63,473	0.82	0.67, 0.99	180	36,028	0.78	0.61, 0.99	97	27,445	0.85	0.62, 1.17
$F \geq 3$	500	37,785	1.09	0.92, 1.29	341	25,101	0.99	0.80, 1.23	159	12,684	1.29	0.98, 1.69
P-trend			0.02				0.23				0.01	
Lung cancer (never smokers only)												
$Q = 1$ (referent)	30	29,333	1		11	10,721	1		19	18,612	1	
$Q = 2$	21	26,400	1.49	0.75, 2.94	10	12,633	1.14	0.41, 3.16	11	13,767	1.75	0.71, 4.34
$Q \geq 3$	12	22,277	1.82	0.71, 4.68	10	14,802	1.75	0.60, 5.09	2	7,475	1.65	0.26, 10.35
P-trend			0.18				0.31				0.31	
$F < 1$ (referent)	17	36,958	1		9	14,512	1		8	22,446	1	
$F = 1$–2	21	28,775	1.37	0.70, 2.68	9	15,953	0.89	0.32, 2.50	12	12,822	1.77	0.74, 4.21
$F \geq 3$	25	12,277	1.60	0.77, 3.35	13	7,691	0.95	0.34, 2.61	12	4,586	2.32	0.77, 6.95
P-trend			0.24				0.96				0.18	

Table continues

risk reduction. To address residual confounding by smoking, we repeated the lung cancer analyses in never smokers alone; among all participants and among men, light drinkers had a significantly lower risk than never drinkers; however, linear trends and quadratic effects were not significant. When the lung cancer analyses were repeated among current smokers alone, results were similar to those conducted in the full cohort (data not shown).

Alcohol consumption quantity and frequency among current drinkers

The age-adjusted Spearman correlation between quantity and frequency was 0.09 in men and 0.07 in women. Among current drinkers, higher quantity was associated with higher risk of all-site cancer mortality. As quantity increased from 1 drink on drinking days to $\geq$3 drinks on drinking days, risk of all-site cancer mortality increased 22% among all participants, with a significant 24% increase among men and a nearly significant 18% increase among women (Table 3). As drinking frequency increased from $<$1 drinking day per week to $\geq$3 drinking days per week, risk of all-site cancer mortality increased 14% among all participants, driven by a 32% increase among women.

Similar findings were seen for lung cancer mortality. As quantity increased, risk of lung cancer mortality significantly increased, by 44% among all participants and 48% among men. As frequency increased, risk of lung cancer mortality significantly increased by 29% among women, and there was a significant quadratic effect among men ($P = 0.03$). When analyses were repeated among participants who had never smoked, results were null; however, the observed relative risks were generally consistent with higher risk from quantity among men and higher risk from both quantity and frequency among women. When the lung cancer analyses were repeated among current smokers alone, results were similar to those conducted in the full cohort (data not shown).

Alcohol quantity was also associated with risk of colorectal cancer mortality in women. As quantity increased, the

Table 3. Continued

Cancer Site and Drinking Pattern[c]	All Participants				Men				Women			
	No. of Deaths	Total No. of Persons	RR	95% CI	No. of Deaths	Total No. of Persons	RR	95% CI	No. of Deaths	Total No. of Persons	RR	95% CI
Colorectal cancer												
$Q = 1$ (referent)	140	54,986	1		75	22,352	1		65	32,634	1	
$Q = 2$	85	56,651	0.85	0.63, 1.17	51	28,143	0.76	0.50, 1.16	34	28,508	0.99	0.64, 1.52
$Q \geq 3$	82	61,730	1.06	0.75, 1.50	58	40,267	0.81	0.52, 1.25	24	21,463	1.93	1.17, 3.18
P-trend			0.67				0.44				0.03	
$F < 1$ (referent)	93	72,109	1		41	29,633	1		52	42,476	1	
$F = 1$–2	100	63,473	1.16	0.84, 1.59	67	36,028	1.22	0.80, 1.87	33	27,445	1.05	0.64, 1.72
$F \geq 3$	114	37,785	1.21	0.88, 1.67	76	25,101	1.23	0.80, 1.90	38	12,684	1.18	0.73, 1.91
P-trend			0.36				0.51				0.52	
Prostate cancer (men) or breast cancer (women)												
$Q = 1$ (referent)					85	22,352	1		103	32,634	1	
$Q = 2$					52	28,143	0.93	0.61, 1.41	65	28,508	0.84	0.57, 1.23
$Q \geq 3$					53	40,267	0.90	0.58, 1.39	37	21,463	0.72	0.45, 1.16
P-trend							0.76				0.13	
$F < 1$ (referent)					40	29,633	1		80	42,476	1	
$F = 1$–2					64	36,028	1.70	1.09, 2.64	61	27,445	1.00	0.67, 1.50
$F \geq 3$					86	25,101	1.55	1.01, 2.38	64	12,684	1.44	0.96, 2.17
P-trend							0.25				0.06	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Pooled data from the 1988, 1990, 1991, and 1997–2004 administrations of the National Health Interview Survey, with follow-up through 2006.

[b] Relative risks were adjusted for race/ethnicity, education, region, marital status, smoking status (including tertiles of smoking intensity among current smokers), body mass index, and gender and mutually adjusted for either quantity or frequency (as appropriate).

[c] *F*, frequency (average number of drinking days per week); *Q*, quantity (number of drinks consumed, on average, on drinking days).

[d] *P* for linear trend based on the adjusted Wald *F* test.

risk of colorectal cancer almost doubled among women; there was no association among men.

The association of quantity and frequency with prostate cancer was complex. There was a significant nonlinear association of frequency with risk, such that men who drank 1–2 days per week had a 70% increased risk of prostate cancer, while those who drank ≥3 days per week had a 55% increased risk (quadratic effect: $P = 0.03$). No association was seen with quantity.

Although there was no significant association of quantity with risk of breast cancer mortality, there was a tendency toward increased risk among women who drank more frequently.

DISCUSSION

In this prospective, pooled analysis of data from 11 administrations of a nationally representative survey representing over 8,000 cases of cancer mortality, higher-quantity drinking and higher-frequency drinking were independently associated with increased risk of all-site cancer mortality and lung cancer mortality among all participants. Quantity conferred greater risk in men, while frequency was more important in women. Higher-quantity drinking was associated with increased risk of colorectal cancer in women, and higher-frequency drinking was associated with increased risk of prostate cancer and possibly breast cancer.

The increased risk of all-site cancer mortality among men associated with higher-quantity drinking and the increased risk in women associated with higher-frequency drinking generally confirmed our previous findings that quantity and frequency had gender-specific effects on all-site cancer mortality (2). The greater importance of quantity in men versus frequency in women may be explained in part by women's tendency to be lighter drinkers with a comparatively truncated range of total intake.

We addressed the possibility that residual confounding by smoking might account for our lung cancer results, an ongoing debate in the alcohol epidemiology literature (12, 13). We repeated analyses within our cohorts' subpopulation of never smokers, which included substantially fewer deaths. In those analyses, results for quantity and frequency were null; however, point estimates suggested increased risk with quantity in men and women and with frequency in women. Interpretation is difficult given the limited statistical power due to the small numbers of deaths among never smokers, with resultant wide confidence intervals.

Higher-quantity drinking was associated with an almost doubled risk of colorectal cancer mortality in women. There was no effect of frequency in either gender, nor was there an effect of total alcohol consumption. This may be due to the relatively small numbers of colorectal cancer deaths in our sample, leading to wide confidence intervals around point estimates that, at least for men, tended to point in opposite directions—that is, toward lower risk for quantity and higher risk for frequency. Our results underscore the need for well-powered studies of associations between drinking patterns and this common malignancy.

Higher frequency of alcohol consumption was associated with increased mortality from prostate cancer. In a previous study, Platz et al. (3) reported increased incidence among men who consumed alcohol 5–6 days per week (but not 7 days per week); risk was attenuated among those with distant metastatic or fatal prostate cancer. They also found increased risk among men who consumed a large quantity of alcohol infrequently (3). These findings and ours suggest that further consideration of drinking quantity and frequency as risk factors for prostate cancer may be warranted.

The relation of total alcohol consumption with breast cancer has been noted for several decades (14). In our study, higher frequency tended to increase the risk of breast cancer mortality, while quantity did not. Results of previous studies (3–7) were variable, and none are comparable to ours, as the outcome in those studies was cancer incidence.

From a methodological standpoint, in studies of alcohol quantity and frequency and cancer risk (and indeed all studies of alcohol and cancer), it is important to note whether the outcome is cancer incidence or cancer mortality. For cancers such as lung cancer, where survival is universally short, incidence approximates mortality; therefore, relations with alcohol quantity and frequency would be expected to be similar. However for cancers of the colorectum, prostate, and breast, relations may differ because of numerous factors (15). This is particularly true where alcohol may differentially affect cancer severity or grade or where early detection itself is associated with alcohol intake.

Note also that associations with quantity and frequency may be obscured when total alcohol consumption is considered. For example, for colorectal cancer among women, we observed a strong relative risk of 1.93 for the highest quantity of drinking, yet results for total alcohol consumption were nonsignificant. Likewise, the relatively strong effect of frequency on risk of prostate cancer mortality was not evident for total alcohol consumption, perhaps because the effects of quantity and frequency tended to point in opposite directions.

Overall, there is a need for better measurement of alcohol consumption in epidemiologic studies (16). Alcohol is often assessed through food frequency questionnaires that do not distinguish former drinkers from lifetime infrequent drinkers, who may have very different risk profiles. While our study focused on patterns of quantity and frequency, a myriad of other patterns could potentially be studied, although not necessarily in the large, nationally representative cohorts represented here. For example, heavy drinking during youth and moderate drinking during adulthood, drinking with meals, beverage type, and cumulative lifetime exposure to alcohol are important areas for future research.

Differential effects of alcohol quantity and frequency are biologically plausible on the basis of more acute (higher quantity) or more chronic (higher frequency) exposure. For example, lower quantities of alcohol are oxidized by alcohol dehydrogenase and higher quantities by alcohol dehydrogenase and cytochrome 2E1, depending on the quantity consumed (17). Acetaldehyde, a metabolic product of alcohol that is also present in alcoholic beverages (18), has been classified as a carcinogen by the International Agency for Research on Cancer (19). Alcohol affects activation and clearance of carcinogens, DNA repair, and metabolism of nutrients and has direct physical effects on tissue and solubility of carcinogens (20). Regular alcohol intake also increases estrogen levels, a primary risk factor for breast cancer (21).

The strengths of our study included the use of a large, nationally representative sample, generated by pooling data from several administrations of the NHIS. Using pooled data, we were able to examine associations between alcohol consumption and specific cancers within a single cohort. Additionally, we were able to categorize nondrinkers as lifetime infrequent drinkers, former drinkers, or lifetime abstainers, making it possible to obtain a relatively pure abstainer referent group.

Our study also had limitations. Alcohol consumption was measured once at baseline, and beverage-specific data were not available in most survey years. Even in our large sample, we were unable to study less common cancers. However, the cancers we did study (lung, colorectal, prostate, and breast) account for approximately half of all cancer deaths in men and women (22).

In conclusion, our study reinforces the importance of considering alcohol quantity and frequency in studies of cancer mortality. Effects of quantity and frequency should be considered separately according to cancer site, since our results suggest that relations may differ by cancer. The outcome—incidence or mortality—should also be considered. Overall, the combination of the sparse literature on alcohol quantity and frequency with the findings of our study suggests that this area provides an opportunity for further research.

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