ORIGINAL INVESTIGATION

Association of Alcohol Intake With Pancreatic Cancer Mortality in Never Smokers

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Background: An international panel of experts characterized the evidence linking alcoholic beverage consumption to pancreatic cancer as limited. Primary concerns include inconsistent results from underpowered studies, residual confounding by smoking, and the question of whether the association varies by type of alcoholic beverage.

Methods: The association of alcohol intake with pancreatic cancer mortality was examined using data from the Cancer Prevention Study II, a prospective study of US adults 30 years and older. Alcohol consumption was self-reported on a 4-page questionnaire in 1982. Based on follow-up through December 31, 2006, there were 6847 pancreatic cancer deaths among 1 030 467 participants. Multivariable-adjusted relative risks (RRs) and 95% confidence intervals (CIs) were computed using Cox proportional hazards regression analysis controlling for age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones, diabetes mellitus, or smoking.

Results: The RRs (95% CIs) of pancreatic cancer mortality associated with current intake of less than 1, 1, 2, 3, and 4 or more drinks per day compared with nondrinkers were 1.06 (0.99-1.13), 0.99 (0.90-1.08), 1.06 (0.97-1.17), 1.25 (1.11-1.42), and 1.17 (1.06-1.29), respectively ($P < .001$ for trend). Consumption of 3 or more drinks per day was associated with pancreatic cancer mortality in never smokers (RR, 1.36; 95% CI, 1.13-1.62) and in ever smokers (RR, 1.16; 95% CI, 1.06-1.27). This association was observed for consumption of liquor (RR, 1.32; 95% CI, 1.10-1.57) but not beer (RR, 1.08; 95% CI, 0.90-1.30) or wine (RR, 1.09; 95% CI, 0.79-1.49).

Conclusion: These results strengthen the evidence that alcohol consumption, specifically liquor consumption of 3 or more drinks per day, increases pancreatic cancer mortality independent of smoking.

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HEAVY ALCOHOL CONSUMPTION causes acute and chronic pancreatitis but has never been linked definitively to pancreatic cancer. Indeed, a panel of experts convened by the International Agency for Research on Cancer in 2009 designated the evidence supporting a causal relationship between alcoholic beverage consumption and pancreatic cancer as limited.[1] The lack of convincing evidence includes concerns about study design, inconsistencies in results of epidemiological studies, and potential residual confounding by smoking. Case-control investigations of this association are limited by sample size, potential recall bias, or possible selection bias owing to the high fatality of pancreatic cancer. Although some individual cohort studies[2-7] and 3 pooled assessments or meta-analyses of prospective studies[8-10] reported statistically significant positive associations between alcohol consumption and pancreatic cancer risk, other cohort studies[11-20] showed no association. However, few studies had adequate statistical power to examine associations for high levels (>2-3 drinks per day) of alcohol consumption. In addition, residual confounding by smoking could explain a weak association, as a high proportion of heavy alcohol drinkers also smoke and tobacco smoking is a well-established modifiable risk factor for pancreatic cancer.[21] Moreover, among the prospective studies[3-7,9,20] that assessed the associations of specific beverage types with risk of pancreatic cancer, some showed a stronger risk for liquor consumption than for beer or wine consumption.[3,5,7,9,20]

The Cancer Prevention Study II (CPS-II) is one of the largest long-term prospective cohort studies conducted to date. In the CPS-II, self-reported alcohol intake, smoking history, and other information was collected from approximately 1.2 million US men and women in 1982. In a pre-

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vious analysis of the CPS-II cohort that assessed the predictors of pancreatic cancer mortality over 14 years of follow-up,[22] there was no association between alcohol intake and pancreatic cancer mortality. In that analysis, consumption exceeding 1 drink per day was the highest category of intake assessed, and no results were reported by beverage type. The present analysis of alcohol intake and pancreatic cancer mortality in the CPS-II is based on almost 7000 pancreatic cancer deaths identified during 24 years of follow-up and is stratified on smoking history and beverage type.

METHODS

CPS-II COHORT

Detailed methods for enrollment of participants and data collection in the CPS-II were reported previously.[23] Briefly, almost 1.2 million adults (508 256 men and 676 206 women) aged 30 to 111 years were enrolled by American Cancer Society volunteers in all 50 US states, the District of Columbia, and Puerto Rico and completed a mailed 4-page questionnaire in 1982. The CPS-II is approved by the Institutional Review Board of Emory University, Atlanta, Georgia.

Excluded from this analysis were CPS-II participants who reported a history of cancer other than nonmelanoma skin cancer (n=82 329), did not provide interpretable information on the amount of alcohol intake (n=6877), reported previous but not current alcohol intake (n=18 612), reported implausibly high alcohol intake (ie, ≥30 drinks per day, which in the Third National Health and Nutrition Examination Survey[24] is at the highest 0.1 percentile of intake) (n=425), or did not provide interpretable information on smoking (n=45 752). Included in the analysis were 453 770 men and 576 697 women.

ASSESSMENT OF ALCOHOL INTAKE AND OTHER RISK FACTORS

The 1982 CPS-II baseline self-administered questionnaire queried participants for information on height and weight; dietary intake of major food groups; demographic, medical, occupational, and behavioral factors; and a detailed history of current and past use of cigarettes (and in men the use of cigars, pipes, and smokeless tobacco). Current alcohol consumption was assessed by the question, "How many cups, glasses or drinks of these beverages do you usually drink a day, and for how many years?" Intake amounts of beer, wine, and liquor were assessed separately. If alcohol intake had changed in the previous 10 years (ie, before enrollment), participants were asked to record their previous amount of consumption for each beverage type. If the intake of a beverage type was less than once per day but at least 3 times per week, participants were asked to write in "½" as their daily consumption.

Nondrinkers were those who wrote "0" intake or left blank the amount for current and previous consumption of all 3 types of alcoholic beverages. Former drinkers were those who indicated 0 intake or left blank the amount for current intake of all 3 beverages but provided information on the previous amount for any type. Current occasional users were those who reported drinking at least 1 type of alcoholic beverage at a level of less than 1 drink per day and did not report consumption of 1 or more drinks per day for any type of alcoholic beverage. For current consumers of 1 or more drinks per day, the total number of drinks per day was computed by summing the intake of all 3 types of alcoholic beverages for which 1 or more drinks per day were reported.

The study questionnaire did not explicitly instruct participants on how to report nonconsumption of any alcoholic beverage. In this analysis, 394 032 participants left the entire alcohol section blank on the 1982 questionnaire, and blank responses were considered to represent nonconsumption. A subcohort (n=166 816) of 1 030 467 CPS-II participants included in this analysis also reported their alcohol intake in 1992-1993 (using the modified Block Food Frequency Questionnaire[25]) when they reenrolled in the CPS-II nutrition cohort. Of the participants who left the entire alcohol section blank in 1982 and responded to the 1992-1993 questionnaire (n=50 293), 74.6% (n=37 502) reported drinking less often than weekly, suggesting that a blank response in 1982 usually but not always indicated no regular alcohol consumption.

MORTALITY FOLLOW-UP

Vital status of the CPS-II participants was determined using 2 approaches. First, in September 1984, 1986, and 1988, American Cancer Society volunteers made personal inquiries to determine whether the participants they had enrolled were alive or dead, and they recorded the dates and places of deaths. Reported deaths were verified by obtaining death certificates. At completion of the 1988 follow-up, vital status was known for 98.2% of the cohort. Second, linkage to the National Death Index was used to identify deaths that occurred between September 1988 and December 2006 and to identify deaths among 21 704 participants lost to follow-up between 1982 and 1988. Death certificates or codes for the cause of death were obtained for more than 99% of all known deaths.

In the United States, more than 97% of pancreatic cancers originate from exocrine cells.[26] In the CPS-II, the underlying cause of death was coded as pancreatic cancer, consistent with the *International Classification of Diseases* (*ICD*) (*ICD-9* codes 157.0-157.9 or *ICD-10* codes C25.0-C25.9).[27,28] Twenty-four participants who were known to have died of endocrine pancreatic cancer (*ICD-9* code 157.4 and *ICD-10* code 25.4) were not counted as pancreatic cancer deaths in this analysis. The total number of pancreatic cancer deaths was 6847 (3443 men and 3404 women).

STATISTICAL ANALYSIS

Nondrinkers were compared with current drinkers, who were categorized according to their mean daily alcohol intake (ie, occasional, 1, 2, 3, or ≥4 drinks per day). In the United States, a standard alcoholic drink is usually defined as 12 oz (336 g) of regular beer, 5 oz (140 g) of wine (12% alcohol), or 1.5 oz (42 g) of 80-proof distilled liquor, and it is estimated that each of these "drinks" contains about 0.6 oz (14 g) of pure ethanol.[29] Smoking history was categorized as never smoker, former cigarette, former cigar or pipe, current cigarette, or current cigar or pipe. Current cigarette use was subcategorized based on the amount (<20 or ≥20 cigarettes smoked per day) and duration (<35 or ≥35 years), while former cigarette use was subcategorized by the length of time since quitting (<10, 10 to <20, or ≥20 years), resulting in 13 smoking categories. Men who smoked both cigarettes and cigars or pipes were assigned to the highest applicable risk category (current cigarette smoker, then current cigar or pipe smoker, then former cigarette smoker, and then former cigar or pipe smoker). All other variables were classified into logical categories, and categories for missing data were included for each covariate.

Person-years of follow-up were computed for each participant as the length of time since completion of the baseline questionnaire until the date of death or December 31, 2006. Cox proportional hazards regression models[30] were used to

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Table 1. Age-Adjusted Selected Baseline Characteristics by Alcohol Intake[a]

Characteristic	No. of Participants[b]	Alcohol Intake, Drinks per Day: Nondrinker	Occasional[c]	1	2	3	≥4
Men							
	(n=453 770)	(n=207 522)	(n=97 550)	(n=41 837)	(n=39 964)	(n=22 350)	(n=44 547)
Age, mean (SD), y	. . .	58.1 (10.4)	56.3 (9.7)	56.9 (9.8)	56.7 (9.5)	56.1 (9.4)	55.8 (9.4)
Body mass index, mean (SD)	. . .	26.0 (3.6)	26.0 (3.3)	25.6 (3.1)	25.8 (3.1)	25.8 (3.3)	26.0 (3.4)
Race/ethnicity, %							
White	427 606	45.3	21.5	9.4	9.0	5.0	9.9
Black	16 162	55.7	21.0	6.1	5.2	3.3	8.8
Other or unknown	10 002	49.4	21.8	8.0	7.0	4.1	9.6
Education, %							
<High school	68 851	58.6	17.8	5.8	5.5	3.3	9.0
High school graduate	89 978	50.5	20.2	7.6	7.6	4.3	9.9
Some college	122 101	44.4	22.1	9.1	9.0	5.1	10.3
College graduate	166 829	38.3	23.5	11.7	10.9	5.9	9.8
Marital status, %							
Single	9384	48.0	21.2	8.1	7.5	4.5	10.6
Married	426 113	45.8	21.6	9.3	8.8	4.9	9.6
Separated or divorced	9257	36.3	22.3	8.8	9.6	6.4	16.7
Widowed	6656	50.1	18.6	7.9	8.0	4.8	10.5
Smoking status, %							
Never	119 350	59.8	20.0	7.5	5.4	2.6	4.7
Current cigarette	110 190	39.1	20.6	8.3	10.1	6.5	15.4
Former cigarette	167 457	41.3	22.8	10.5	10.1	5.5	9.9
Ever pipe or cigar	43 703	41.1	23.4	11.3	9.9	5.2	9.1
Ever smoker, unclassified	13 070	45.8	20.1	8.8	8.8	5.1	11.4
Personal history of diabetes mellitus, %							
No	428 690	44.8	21.8	9.4	9.0	5.0	10.0
Yes	25 080	61.7	16.2	6.1	5.7	3.5	6.8
Personal history of gallstones, %							
No	431 802	45.4	21.5	9.3	8.9	5.0	10.0
Yes	21 968	53.1	20.9	8.2	7.5	3.5	6.7
Family history of pancreatic cancer, %							
No	448 628	45.8	21.5	9.2	8.8	4.9	9.8
Yes	5142	41.6	22.7	10.2	9.5	5.6	10.4
Women							
	(n=576 697)	(n=360 501)	(n=118 585)	(n=35 878)	(n=30 812)	(n=12 452)	(n=18 469)
Age, mean (SD), y	. . .	56.8 (11.3)	54.6 (10.3)	55.3 (10.3)	55.3 (9.8)	54.5 (9.6)	54.6 (10.0)
Body mass index, mean (SD)	. . .	25.1 (4.7)	24.2 (4.1)	23.4 (3.6)	23.3 (3.6)	23.5 (3.8)	23.6 (3.9)
Race/ethnicity, %							
White	536 234	61.7	20.9	6.4	5.5	2.2	3.2
Black	27 416	74.1	15.5	3.4	2.8	1.4	2.8
Other or unknown	13 047	72.5	16.4	4.1	3.1	1.3	2.5
Education, %							
<High school	74 646	79.6	12.1	2.9	2.4	1.1	1.9
High school graduate	175 558	67.0	19.2	5.0	4.3	1.8	2.7
Some college	173 641	57.8	23.0	6.9	6.2	2.5	3.7
College graduate	144 757	53.1	24.1	8.7	7.2	2.8	4.0
Marital status, %							
Single	23 436	63.5	20.8	5.6	4.6	2.2	3.3
Married	438 726	61.4	21.0	6.5	5.6	2.2	3.2
Separated or divorced	33 009	56.6	23.8	6.2	6.1	2.7	4.6
Widowed	77 847	70.6	16.6	4.6	4.0	1.6	2.5
Smoking status, %							
Never	322 472	72.9	17.0	4.5	2.9	1.0	1.6
Current cigarette	121 186	50.1	23.5	7.6	8.6	4.2	6.1
Former cigarette	121 809	48.2	26.9	9.3	8.3	3.1	4.4
Ever smoker, unclassified	11 230	53.4	23.1	7.4	7.8	3.2	5.1
Personal history of diabetes mellitus, %							
No	551 714	61.6	21.0	6.4	5.5	2.2	3.3
Yes	24 983	81.7	10.8	2.5	2.4	1.0	1.6
Personal history of gallstones, %							
No	513 275	61.5	20.9	6.4	5.6	2.3	3.3
Yes	63 422	70.6	17.8	4.6	3.6	1.4	2.1
Family history of pancreatic cancer, %							
No	568 728	62.6	20.5	6.2	5.3	2.2	3.2
Yes	7969	58.9	22.8	6.5	5.7	2.5	3.5

Abbreviation: Ellipsis, not applicable.

[a] Data are from the Cancer Prevention Study, 1982 to 2006. Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] The numbers of men and women for each characteristic may not sum to the total number because of missing data.

[c] Occasional drinkers are defined as those participants who reported drinking at least 1 type of alcoholic beverage at a level of less than 1 drink per day and did not report consumption of 1 or more drinks per day for any type of alcoholic beverage.

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Table 2. Age-Adjusted and Multivariable-Adjusted Relative Risks for the Association of Alcohol Intake With Pancreatic Cancer Mortality[a]

Alcohol Intake, Drinks per Day	No. of Deaths	Total Person-Years	Age-Adjusted Relative Risk (95% CI)[b]	Multivariable-Adjusted Without Smoking Relative Risk (95% CI)[c]	Multivariable-Adjusted With Smoking Relative Risk (95% CI)[d]
			Men		
Nondrinker	1498	3 870 330	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Occasional	737	1 943 555	1.04 (0.95-1.13)	1.05 (0.96-1.15)	1.03 (0.94-1.13)
1	321	833 180	1.02 (0.90-1.15)	1.05 (0.93-1.18)	1.03 (0.91-1.16)
2	311	786 741	1.06 (0.94-1.20)	1.09 (0.96-1.23)	1.04 (0.92-1.18)
3	216	438 416	1.37 (1.19-1.58)	1.41 (1.22-1.63)	1.31 (1.14-1.52)
≥4	360	849 924	1.22 (1.09-1.37)	1.24 (1.11-1.40)	1.14 (1.01-1.28)
P for trend	. . .	. . .	<.001	<.001	.002
			Women		
Nondrinker	2083	7 479 594	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Occasional	716	2 582 559	1.10 (1.01-1.19)	1.13 (1.04-1.23)	1.08 (0.99-1.18)
1	189	775 475	0.93 (0.80-1.08)	0.98 (0.85-1.14)	0.92 (0.79-1.07)
2	202	659 397	1.18 (1.02-1.36)	1.24 (1.07-1.43)	1.10 (0.95-1.28)
3	80	264 350	1.24 (0.99-1.55)	1.30 (1.04-1.62)	1.11 (0.89-1.39)
≥4	134	390 330	1.39 (1.17-1.66)	1.45 (1.21-1.73)	1.25 (1.05-1.50)
P for trend	. . .	. . .	<.001	<.001	.02
			Total Cohort		
Nondrinker	**3581**	**11 349 924**	1.00 [Reference]	1.00 [Reference]	1.00 [Reference]
Occasional	**1453**	**4 526 114**	1.07 (1.00-1.13)	1.09 (1.03-1.16)	1.06 (0.99-1.13)
1	**510**	**1 608 655**	0.99 (0.90-1.08)	1.03 (0.94-1.13)	0.99 (0.90-1.08)
2	**513**	**1 446 138**	1.11 (1.01-1.22)	1.15 (1.05-1.26)	1.06 (0.97-1.17)
3	**296**	**702 766**	1.34 (1.19-1.51)	1.39 (1.23-1.56)	1.25 (1.11-1.42)
≥4	**494**	**1 240 254**	1.27 (1.16-1.40)	1.31 (1.19-1.44)	1.17 (1.06-1.29)
P for trend	. . .	. . .	<.001	<.001	<.001

Abbreviations: CI, confidence interval; ellipsis, not applicable.
[a] Data are from the Cancer Prevention Study, 1982 to 2006. *P* for trend was computed using a score variable for each level of alcohol intake.
[b] Adjusted for age and sex.
[c] Adjusted for age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones or diabetes mellitus.
[d] Adjusted for age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones, diabetes mellitus, or smoking.

compute adjusted relative risks (RRs) and 95% confidence intervals (CIs). In all analyses, the reference group was nondrinkers. All models were adjusted for age using the stratified Cox proportional hazards regression model procedure and for sex in the analyses of men and women combined. Additional multivariable-adjusted models also included dummy variables for race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones or diabetes mellitus. To assess confounding by smoking, dummy variables for categories of smoking history were then added. These covariates were included because they were previously shown to be associated with pancreatic cancer mortality in this cohort.[22] Adjustment for red meat intake and consumption of processed meat, fruits, and vegetables did not confound associations and were not included in the final model. *P* values for trend were determined using a continuous score variable for each level of alcohol intake. The proportional hazards assumption was tested and confirmed.

Effect modification by smoking status (never vs ever) was assessed by computing *P* values for multiplicative interactions using likelihood ratio test comparing Cox proportional hazards multivariable models with and without cross-product terms for current alcohol intake and smoking status. Never smokers were those who reported no history of smoking cigarettes, cigars, or pipes, whereas ever smokers were those who reported past or current use of these tobacco products.

Associations of specific types of alcoholic beverages with pancreatic cancer were examined in separate models for beer-only, wine-only, and liquor-only drinkers compared with nondrinkers. Participants who reported consuming more than 1 type of beverage were excluded from this analysis.

RESULTS

Among 453 770 men and 576 697 women included in this study, 45.7% of men and 62.5% of women were nondrinkers. **Table 1** gives sex-specific age-adjusted baseline characteristics across categories of alcohol intake. For men and women, the mean age at baseline was approximately 2 years older in nondrinkers compared with those who reported drinking at least 4 drinks per day. For men, there was no meaningful difference in the mean body mass index across alcohol intake categories, whereas for women the mean body mass index was slightly higher in nondrinkers compared with current drinkers. For men and women, a higher proportion of black participants were nondrinkers than white participants, as were participants with less than a high school education, those who had been widowed, those who were never smokers, and those who had a history of diabetes or gallstones.

A positive association was noted between the amount of alcohol intake and pancreatic cancer mortality in age-adjusted analyses and in multivariable-adjusted analyses, although associations were attenuated after adjustment for smoking history (**Table 2**). The analyses of men and of

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Table 3. Smoking-Stratified Multivariable-Adjusted Relative Risks for the Association of Alcohol Intake With Pancreatic Cancer Mortality[a]

Alcohol Intake, Drinks per Day	Never Smokers		Ever Smokers		
	No. of Deaths	Relative Risk (95% CI)[b]	No. of Deaths	Relative Risk (95% CI)[b]	Relative Risk (95% CI)[c]
Men					
Nondrinker	489	1.00 [Reference]	1009	1.00 [Reference]	1.00 [Reference]
Occasional	155	0.98 (0.82-1.18)	582	1.05 (0.95-1.16)	1.05 (0.95-1.16)
1	64	1.06 (0.82-1.38)	257	1.02 (0.89-1.17)	1.02 (0.89-1.17)
2	39	0.91 (0.66-1.27)	272	1.08 (0.94-1.24)	1.06 (0.93-1.22)
≥3	76	1.36 (1.07-1.73)	500	1.24 (1.11-1.38)	1.18 (1.06-1.31)
P for trend	. . .	.08	. . .	<.001	.007
Women					
Nondrinker	1303	1.00 [Reference]	780	1.00 [Reference]	1.00 [Reference]
Occasional	314	1.13 (1.00-1.28)	402	1.01 (0.90-1.15)	1.03 (0.91-1.16)
1	77	1.05 (0.84-1.33)	112	0.82 (0.67-1.01)	0.83 (0.68-1.01)
2	53	1.10 (0.84-1.45)	149	1.10 (0.92-1.32)	1.07 (0.90-1.28)
≥3	55	1.33 (1.01-1.74)	159	1.18 (1.00-1.41)	1.12 (0.94-1.33)
P for trend	. . .	.02	. . .	.13	.38
Total Cohort					
Nondrinker	**1792**	1.00 [Reference]	**1789**	1.00 [Reference]	1.00 [Reference]
Occasional	**469**	1.08 (0.97-1.20)	**984**	1.04 (0.96-1.12)	1.04 (0.96-1.13)
1	**141**	1.06 (0.90-1.27)	**369**	0.95 (0.85-1.06)	0.95 (0.85-1.07)
2	**92**	1.02 (0.83-1.26)	**421**	1.09 (0.98-1.21)	1.07 (0.96-1.19)
≥3	**131**	1.36 (1.13-1.62)	**659**	1.22 (1.12-1.34)	1.16 (1.06-1.27)
P for trend	. . .	.004	. . .	<.001	.006

Abbreviations: CI, confidence interval; ellipsis, not applicable.
[a] Data are from the Cancer Prevention Study, 1982 to 2006. *P* for trend was computed using a score variable for each level of alcohol intake.
[b] Adjusted for age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones or diabetes mellitus.
[c] Adjusted for age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones, diabetes mellitus, or smoking.

men and women combined showed statistically significantly increased risks of pancreatic cancer mortality associated with consumption of 3 drinks per day and of 4 or more drinks per day, whereas for women the RR estimates were significantly elevated for consumption of 4 or more drinks per day. In a sensitivity analysis, we excluded 394 032 participants (2456 pancreatic cancer deaths) categorized as nondrinkers who provided no information on current alcohol intake, and the RRs (95% CIs) of pancreatic cancer mortality associated with occasional, 1, 2, 3, and 4 or more drinks per day compared with nondrinkers were 0.98 (0.91-1.07), 0.92 (0.83-1.03), 1.00 (0.90-1.11), 1.18 (1.03-1.35), and 1.10 (0.98-1.22), respectively ($P=.02$ for trend). After excluding the first 5 years of follow-up, the RRs (95% CIs) of pancreatic cancer mortality associated with occasional, 1, 2, 3, and 4 or more drinks per day compared with nondrinkers were 1.08 (1.01-1.16), 1.02 (0.92-1.12), 1.10 (0.99-1.22), 1.32 (1.16-1.50), and 1.17 (1.05-1.30), respectively ($P<.001$ for trend) in men and women combined.

In analyses stratified on smoking status, alcohol intake was associated with an excess risk of pancreatic cancer mortality in never smokers and in ever smokers (**Table 3**). In never smokers, there was a 36% higher risk of pancreatic cancer mortality associated with consumption of 3 or more drinks per day compared with nondrinkers for men and women combined, whereas in ever smokers there was a 16% higher risk after adjustment for smoking history and other covariates. There was no statistically significant interaction between alcohol consumption and smoking status ($P=.58$ for interaction).

No association of beer or wine consumption with pancreatic cancer mortality was observed (**Table 4**). However, compared with nondrinkers, consumption of 3 or more drinks of liquor per day was associated with a significantly elevated risk of pancreatic cancer mortality in the total cohort, and consumption of 2 or more drinks of liquor per day was associated with an increased risk in never smokers and in ever smokers.

COMMENT

In this large prospective study, alcohol intake of 3 or more drinks per day consumed as liquor was associated with an excess risk of pancreatic cancer mortality after adjustment for smoking history, as well as in lifelong never smokers. The size and follow-up duration of this study help to resolve concerns about inconsistencies observed in other investigations of the alcohol consumption–pancreatic cancer association owing to underpowered studies and the potential for residual confounding by smoking.

As aforementioned, many other prospective cohort investigations have found no association between alcohol intake and pancreatic cancer risk. However, few investigators were able to examine the relationship for high levels of alcohol consumption. In one of the larg-

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Table 4. Multivariable-Adjusted Relative Risks for the Association of Beer-Only, Wine-Only, or Liquor-Only Alcohol Intake With Pancreatic Cancer Mortality[a]

Alcohol Intake, Drinks per day	Beer Only		Wine Only		Liquor Only	
	No. of Deaths	Relative Risk (95% CI)	No. of Deaths	Relative Risk (95% CI)	No. of Deaths	Relative Risk (95% CI)
Never Smokers[b]						
Nondrinker	1792	1.00 [Reference]	1792	1.00 [Reference]	1792	1.00 [Reference]
Occasional	59	1.03 (0.79-1.33)	131	1.01 (0.84-1.21)	76	1.20 (0.96-1.52)
1	19	0.91 (0.58-1.44)	41	1.05 (0.77-1.44)	23	0.87 (0.58-1.32)
≥2	25	1.09 (0.73-1.63)	24	0.94 (0.63-1.40)	41	1.47 (1.08-2.01)
P for trend	. . .	.82	. . .	.99	. . .	.03
Ever Smokers[c]						
Nondrinker	1789	1.00 [Reference]	1789	1.00 [Reference]	1789	1.00 [Reference]
Occasional	172	1.02 (0.87-1.20)	155	1.03 (0.87-1.22)	191	0.97 (0.84-1.13)
1	60	0.86 (0.66-1.11)	58	0.90 (0.69-1.18)	104	0.94 (0.77-1.15)
≥2	177	1.08 (0.92-1.26)	65	0.98 (0.76-1.26)	247	1.18 (1.03-1.35)
P for trend	. . .	.65	. . .	.71	. . .	.07
Total Cohort[c]						
Nondrinker	**3581**	1.00 [Reference]	**3581**	1.00 [Reference]	**3581**	1.00 [Reference]
Occasional	**231**	1.02 (0.89-1.17)	**286**	1.02 (0.90-1.15)	**267**	1.03 (0.91-1.17)
1	**79**	0.87 (0.70-1.09)	**99**	0.96 (0.79-1.18)	**127**	0.94 (0.78-1.12)
2	77	1.08 (0.86-1.35)	50	0.91 (0.68-1.20)	156	1.15 (0.98-1.35)
≥3	125	1.08 (0.90-1.30)	39	1.09 (0.79-1.49)	132	1.32 (1.10-1.57)
P for trend	. . .	.54	. . .	.91	. . .	.006

Abbreviations: CI, confidence interval; ellipsis, not applicable.

[a] Data are from the Cancer Prevention Study, 1982 to 2006. *P* for trend was computed using a score variable for each level of alcohol intake.

[b] Relative risks adjusted for age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones or diabetes mellitus.

[c] Relative risks adjusted for age, sex, race/ethnicity, education, marital status, body mass index, family history of pancreatic cancer, and personal history of gallstones, diabetes mellitus, or smoking.

est cohort studies published to date, which included 1149 pancreatic cancer cases, the RR of pancreatic cancer associated with consumption of at least 3 drinks per day was 1.5 (95% CI, 1.2-1.9) based on 126 cases in that category of consumption.[7] In a large pooled analysis of 14 other cohort studies, which included 2187 incident pancreatic cancer cases, the RR of pancreatic cancer associated with consumption of at least 30 g/d of ethanol (ie, ≥2 drinks per day)—the highest alcohol consumption category considered—was 1.22 (95% CI, 1.03-1.45) based on 243 cases in that category.[8] Another pooled analysis of nested case-control studies reported a nonsignificant elevated risk of pancreatic cancer associated with consumption of 60 g/d of ethanol (RR, 1.38; 95% CI, 0.86-2.23) based on 47 cases and 35 controls.[9] Similarly, a meta-analysis[10] of cohort studies showed no association of pancreatic cancer with "moderate" alcohol consumption (ie, >0 to <3 drinks per day) but demonstrated a 26% excess risk associated with heavy consumption (ie, ≥3 drinks per day). Overall, these findings are similar to those herein and suggest that if a causal association exists it is with the intake of at least 2 to 3 drinks per day.

Statistical power constraints also limited the ability of other studies to examine the association between alcohol intake and pancreatic cancer risk in lifelong never smokers. Among other prospective investigations that examined this relationship in never smokers, 2 studies[14,17] reported no significant association of alcohol intake with pancreatic cancer risk overall or in never smokers. In 4 prospective studies,[5-7,9] including the aforementioned large study by Jiao et al,[7] nonsignificant positive associations between alcohol intake and pancreatic cancer were seen in never smokers. However, in those studies, the number of pancreatic cancer cases in the subgroup of never smokers who consumed 2 or more drinks per day was small (ie, ≤27). By contrast, the subgroup of never smokers in the CPS-II who reported consumption of 3 or more drinks per day included 131 pancreatic cancer cases. The almost 1.4-fold higher risk (95% CI, 1.13-1.62) in this subgroup is particularly informative and provides strong evidence for an association of alcohol intake with pancreatic cancer independent of smoking.

In the CPS-II, the excess risk of pancreatic cancer mortality was largely confined to those who reported heavy consumption of liquor but not beer or wine. These findings are consistent with 5 of 7 other prospective studies[3-7,9,20] that examined risk according to specific beverage types (results differed in 2 studies[4,6]). Most important, the large size of this study allowed for a stratified analysis of beverage type in which participants who consumed more than 1 type were excluded, whereas in other investigations the analyses adjusted for type of beverage consumed, which could result in residual confounding. Reasons for an association of pancreatic cancer mortality with liquor consumption but not wine or beer intake are unclear. There is evidence that a drink of liquor as actually consumed contains substantially more alcohol than a drink of beer or

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wine.[31] Therefore, a specificity association between liquor consumption and pancreatic cancer risk might reflect higher alcohol consumption rather than differences in potentially nonalcoholic toxic components among beverage types.

The biologic mechanism underlying an association between alcohol consumption and pancreatic cancer is not fully understood, although it is well recognized that long-term heavy intake causes chronic alcoholic pancreatitis,[32] an established risk factor for pancreatic cancer.[21] In addition, ethanol is metabolized in the pancreas via oxidative and nonoxidative pathways.[33] Go et al[34] hypothesized several mechanisms by which the metabolites of these pathways might affect inflammation and carcinogenesis, including activation of nuclear transcription factors, increased production of reactive oxygen species, and dysregulation of cell proliferation and apoptosis.

The major strengths of this study include its size, availability of detailed exposure data, and length of follow-up, which allowed for an analysis over a wide range of intake and with stratification on smoking and beverage type. Despite these strengths, the principal limitations should be recognized. The validity of the information on alcohol consumption in the CPS-II was not evaluated directly, although consumption is associated with higher death rates from injuries, liver cancer, colorectal cancer, head and neck cancers, and cirrhosis of the liver and with lower death rates from coronary heart disease, as reported elsewhere.[35] In addition, participants might have underreported their intake, and a single assessment of alcohol intake at baseline does not capture changes in consumption during the follow-up period; some drinkers might have reduced their alcohol intake as they aged. These limitations would probably lead to attenuation of an association, as any misclassification is likely to be nondifferential between those who died of pancreatic cancer and those who did not. Similarly, the cause of death might be misclassified, as pancreatic cancer is often misreported on the death certificate[36] and there is some evidence that this misclassification results in attenuated associations.[37]

Alcoholic beverage consumption—a modifiable lifestyle factor—is causally related to several cancers, including oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast.[1] Findings from the prospective study presented herein strongly support the hypothesis that alcohol consumption, in particular heavy intake, also is an independent risk factor for pancreatic cancer, the fourth most common cause of cancer mortality in the United States.[21] These results underscore the importance of adhering to the following guideline for cancer prevention by the American Cancer Society: "If you drink alcoholic beverages, limit consumption."[38(p264)]

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