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Original Contribution

Alcohol Use and Risk of Pancreatic Cancer

The NIH-AARP Diet and Health Study

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The epidemiologic evidence for the role of alcohol use in pancreatic cancer development is equivocal. The authors prospectively examined the relation between alcohol use and risk of pancreatic cancer among 470,681 participants who were aged 50–71 years in 1995–1996 in the US National Institutes of Health-AARP Diet and Health Study. The authors identified 1,149 eligible exocrine pancreatic cancer cases through December 2003. Multivariate Cox proportional hazards regression models were used to calculate relative risks and 95% confidence intervals with the referent group being light drinkers (<1 drink/day). The relative risks of developing pancreatic cancer were 1.45 (95% confidence interval (CI): 1.17, 1.80; $P_{trend} = 0.002$) for heavy total alcohol use (≥3 drinks/day, ~40 g of alcohol/day) and 1.62 (95% CI: 1.24, 2.10; $P_{trend} = 0.001$) for heavy liquor use, compared with the respective referent group. The increased risk with heavy total alcohol use was seen in never smokers (relative risk = 1.35, 95% CI: 0.79, 2.30) and participants who quit smoking 10 or more years ago before baseline (relative risk = 1.41, 95% CI: 1.01, 2.00). These findings suggest a moderately increased pancreatic cancer risk with heavy alcohol use, particularly liquor; however, residual confounding by cigarette smoking cannot be completely excluded.

alcohol drinking; cohort studies; pancreatic neoplasms; risk; smoking

Abbreviations: CI, confidence interval; NIH, National Institutes of Health.

Alcohol use has been implicated in the etiology of cancers of the mouth, pharynx and larynx, esophagus, breast, liver, and colorectum (1). The epidemiologic evidence for the role of alcohol use in the etiology of pancreatic cancer is equivocal. At least 60 analytical epidemiologic studies (2–4), including 13 prospective cohort studies (5–17), have examined the association between alcohol use and incidence and/or mortality of pancreatic cancer. Many studies did not find any association (3). Eight studies (7, 10, 17–22) have shown a positive association after adjustment for smoking. Six have shown an increased risk with beer and liquor (10, 17, 19–21, 23), and 4 have shown a reduced risk with white wine (24–27).

As heavy alcohol use is the most common cause of both acute and chronic pancreatitis (28, 29), high levels of alcohol use could plausibly contribute to pancreatic cancer development via pancreatitis (30). The lack of associations between alcohol use and pancreatic cancer risk in the existing studies may reflect methodological difficulties, including small sample size, reverse causation, and selection, recall, and proxy reporting biases, as well as a narrow range of alcohol consumption in the study populations. For 8 studies that have shown positive associations, residual confounding by cigarette smoking may be present because people who drink also tend to smoke and cigarette smoking is a risk factor for pancreatic cancer. Several studies that have investigated alcohol use in never smokers yielded inconsistent findings (14, 17, 23, 24).

To further elucidate the relation between alcohol use and pancreatic cancer risk, we conducted an analysis in the

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National Institutes of Health (NIH)-AARP Diet and Health Study, a cohort of nearly a half million American people who reported a wide range of alcohol consumption. In order to address residual confounding by smoking, we stratified our analysis by smoking status.

MATERIALS AND METHODS

Study population

The NIH-AARP Diet and Health Study is a large prospective cohort study of AARP members established at baseline 1995–1996. Details of the study design and questionnaire have been described elsewhere (31). Briefly, a self-administered baseline questionnaire was mailed to 3.5 million AARP members aged 50–71 years who resided in 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). A total of 617,119 members returned the questionnaires, and 567,169 completed the questionnaire satisfactorily (31). The study was approved by the National Cancer Institute Special Studies Institutional Review Board. Informed consent was obtained from each participant by returning the questionnaire.

We excluded people with duplicate representation ($n = 179$) and those who moved out of the study areas before returning the questionnaire ($n = 321$), died before study entry ($n = 261$), or withdrew ($n = 6$). From the remaining 566,402 participants, we further excluded people who had the questionnaire completed by proxy respondents ($n = 15{,}760$); prevalent cancer cases as identified through cancer registries at baseline ($n = 8{,}583$); and those with extreme energy intake (i.e., more than 2 interquartile ranges above the 75th or below the 25th percentile of Box-Cox log-transformed energy intake, $n = 4{,}792$), missing or conflicting self-reported smoking information ($n = 20{,}169$), self-reported cancer history ($n = 40{,}907$, except for nonmelanoma skin cancer), and less than 1 year of follow-up ($n = 5{,}510$). Our reason for excluding participants who were censored during the first year of follow-up was to minimize the possibility of reverse causation in analyzing alcohol use and pancreatic cancer risk. Our final analytical cohort consisted of 470,681 AARP members, including 280,084 men and 190,597 women.

Cohort follow-up and case ascertainment

Follow-up time was calculated from 1 year after the response to the questionnaire to the date of pancreatic cancer diagnosis, move out of the study areas, death from any cause, or December 31, 2003. The NIH-AARP Diet and Health Study has been following up participants yearly by using the National Change of Address database (US Postal Service) and MaxCoA (Anchor Computer, Inc., Farmingdale, New York). Additional information on change of address was received directly from participants who reported address changes when responding to study mailings, such as follow-up questionnaires or newsletters. In addition, we expanded our cancer registry ascertainment area by 3 states (Arizona, Nevada, and Texas) to capture cancer cases occurring among participants who moved to those states during follow-up. Approximately 4% of participants were lost to follow-up. Vital status was ascertained by annual linkage to the Social Security Administration Death Master File. Incident pancreatic cancer cases were identified by linkage to 11 state cancer registries (32), and fatal cases were identified by linkage to the National Death Index. We included adenocarcinoma of the exocrine pancreas (*International Classification of Diseases for Oncology*, Third Edition, codes C25.0–C25.3 and C25.7–C25.9) and excluded histology types 8150–8155, 8240, 8246, and 8502 because the etiology of these tumors is thought to be different (33). We ascertained 1,149 cases, including 88% incident cases and 12% fatal cases, in the current analysis.

Exposure assessment

At baseline, the study participants completed the self-administered questionnaire that elicited information on demographic factors, smoking, diet, medical history, body weight and height, physical activity, and other health-related behaviors (31). The questionnaire assessed the usual frequency of consumption and portion size of 124 food items (including beer, wine, and liquor) over the previous 12 months (34, 35). Servings of alcohol use per day were computed for total beverages and for each type of alcoholic beverage. One serving (1 drink) was defined on the basis of the US Department of Agriculture's Food Guide Pyramid as 12 fluid ounces of regular beer (12.96 g of alcohol), 5 fluid ounces of wine (13.72 g of alcohol), or 1.5 ounces of 80 proof distilled spirits liquor (13.93 g of alcohol) (36). The Spearman correlation coefficient for alcohol use between the baseline questionnaire and 2 nonconsecutive 24-hour recalls was 0.68 in men and 0.63 in women (37).

Participants reported whether they smoked at least 100 cigarettes during their entire life to distinguish ever smokers from never smokers. Ever smokers reported whether they currently smoked, when they had stopped smoking (<1 year or 1–4, 5–9, or ≥ 10 years ago), and their daily smoking dose (1–10, 11–20, 21–30, 31–40, 41–60, and ≥ 61 cigarettes). Because the questionnaire did not elicit information on smoking duration, we estimated this variable by assuming that 1) all participants started smoking at 18 years of age and 2) the number of years since quit smoking was 2.5, 7, or 15 years for those who stopped smoking 1–4, 5–9, or ≥ 10 years ago, respectively. For former smokers, the duration of smoking was obtained by subtracting the assumed smoking start age from the estimated smoking quit age; for current smokers, the duration was obtained by subtracting the smoking start age from the age at baseline.

Statistical analysis

Cox proportional hazards regression models, with age as the underlying time metric, were used to estimate relative risks and 95% confidence intervals of pancreatic cancer in relation to alcohol use or cigarette smoking (38, 39). We tested the proportional hazards assumption for alcohol use, smoking, and other confounding factors using Grambsch and Therneau's test (40). The dietary variables were energy

adjusted by using the density method. Because the questionnaire queried about alcohol use over the past 12 months before baseline, it was possible that those who reported not drinking alcohol (nondrinkers) included former drinkers, some of whom may have been chronically ill (41). We observed a J-shaped relation between alcohol use and pancreatic cancer in that a slightly higher risk of pancreatic cancer was observed in nondrinkers. We found that the prevalence of diabetes, a putative risk factor for pancreatic cancer, was higher among nondrinkers than drinkers, especially among nondrinkers of beer and nondrinkers among participants who were current smokers or quit smoking recently. Therefore, in order to avoid potential reverse causation bias, we chose light drinkers, that is, those who consumed less than 1 drink per day (>0–0.99), as the reference group. A similar approach has been used in some previous studies (4, 10, 11, 24, 42, 43). Risk of pancreatic cancer was examined by 1 drink (13–14 g of alcohol) increment per day. We then collapsed the categories of alcohol use if the risk estimates were similar: nondrinkers (0 drinks per day), moderate drinkers (1–2.99 drinks per day), and heavy drinkers (≥3 drinks per day). Across these 4 drink categories, we computed age-adjusted incidence rates using direct standardization to the NIH-AARP Diet and Health Study population with a 1-year age interval.

The following confounding variables were included in the multiple covariate-adjusted models, either because they were significantly associated with alcohol use and risk of pancreatic cancer or because their inclusion in the multivariate models changed the risk estimate by more than 10% in the forward stepwise selection: smoking history, total energy intake (kcal/day), energy-adjusted intakes of saturated fat (g/1,000 kcal/day), and red meat (g/1,000 kcal/day). We also included sex (in the sex-combined models), total folate intake (mg/1,000 kcal/day), body mass index (<20, 20–<25, 25–<30, ≥30 kg/m^2, missing), level of physical activity (low, moderate, and high), and self-reported history of diabetes (yes vs. no) in the final models. We created a compound smoking variable with fine categories: never smokers, quit ≥10 years ago and smoked <20 cigarettes/day, quit ≥10 years ago and smoked ≥20 cigarettes/day, quit 5–9 years ago and smoked <20 cigarettes/day, quit 5–9 years ago and smoked ≥20 cigarettes/day, quit 1–4 years ago and smoked <20 cigarettes/day, quit 1–4 years ago and smoked ≥20 cigarettes/day, current smokers with <20 cigarettes/day, and current smokers with ≥20 cigarettes/day. Individual alcoholic beverages were mutually adjusted for each other.

Stratified analyses were performed by sex, type of alcoholic beverage, lifelong smoking status (never vs. ever), the number of years since quit smoking (never, quit 10 or more years ago or longtime former smokers, quit in the past 2–9 years or recent quitters, and current smokers), folate intake (median split, 268 mg/1,000 kcal/day), and history of diabetes. Although we used 3 drinks per day to categorize the moderate versus heavy use of liquor, we used 1 drink per day as a cutoff for beer or wine so as to maintain an adequate number of participants in each category. We carried out the analysis stratified by the number of years since quitting smoking, because previous studies have shown a reduction in pancreatic cancer risk among former smokers with risks approaching that of never smokers within 5–15 years after smoking cessation (44, 45). In our study, compared with never smokers, ever smokers had a relative risk of 1.42 (95% confidence interval (CI): 1.24, 1.61), and recent quitters and current smokers had a relative risk of 1.88 (95% CI: 1.42, 2.50). The relative risk for longtime former smokers was 1.15 (95% CI: 0.997, 1.34) in all participants, 1.05 (95% CI: 0.87, 1.25) in men, and 1.40 (95% CI: 1.09, 1.79) in women. We adjusted for smoking duration and smoking dose in the analyses conducted in ever smokers. The likelihood ratio test was used to test the interaction of alcohol use (4-level drink category) association by sex, smoking history, folate intake, and diabetes. We calculated the *P* value for linear trend using the Wald test by assigning the median value of each drink category (excluding nondrinkers) as a continuous variable in the multivariate models.

We conducted a lag analysis excluding participants who were censored during the first 2 years of follow-up. All analyses were done by using STATA, version 9.0, software (StataCorp LP, College Station, Texas) or SAS, version 9.0, software (SAS Institute, Inc., Cary, North Carolina). All *P* values were 2 sided and considered statistically significant if less than 0.05.

RESULTS

During the average follow-up time of 7.3 years, we identified 748 cases in men and 401 cases in women. The age-standardized incidence rate per 100,000 person-years was 40.2 (95% CI: 35.9, 44.4) among nondrinkers, 32.6 (95% CI: 30.0, 35.1) among light drinkers, 29.9 (95% CI: 25.4, 34.4) among moderate drinkers, and 46.4 (95% CI: 37.7, 55.5) among heavy drinkers. There was no deviation from the proportional hazards assumption for alcohol use, smoking, and other confounding factors.

Table 1 summarizes the means for the continuous characteristics and proportions for the categorical characteristics by sex according to total alcohol use. The mean daily consumption among drinkers was 13.3 g (approximately 1 drink of alcohol). Wine consumption was less frequent than beer or liquor consumption. Heavy drinkers (had ≥3 drinks per day) were less likely to be African Americans or to have self-reported diabetes. They also tended to consume less total fat, saturated fat, and total folate than light drinkers.

Compared with light drinkers, those who consumed 6 or more drinks per day had a relative risk of 1.55 (95% CI: 1.13, 2.13; $P_{trend} = 0.004$) and 3 or more drinks per day had a relative risk of 1.45 (95% CI: 1.17, 1.80; $P_{trend} = 0.002$) (Table 2). We did not detect a significant increased risk with heavy alcohol use in women. Only 2.7% of women were heavy alcohol drinkers, compared with 10.8% of men. Compared with light drinkers of liquor, heavy drinkers of liquor had a 62% increased risk of developing pancreatic cancer (95% CI: 1.24, 2.10; $P_{trend} = 0.001$). The elevated relative risk for heavy liquor use was statistically significant in men but not in women. Beer or wine use was not associated with the risk (Table 3).

Table 1. Means and Proportions of Selected Characteristics of Men and Women According to Total Alcoholic Drinks per Day in the NIH-AARP Diet and Health Study, United States, 1995/1996–2003

Characteristics	Alcoholic Drinks per Day[a]							
	Men (n = 280,084)				Women (n = 190,597)			
	0[b] (None)	>0–0.99 (Light)	1–2.99 (Moderate)	≥3 (Heavy)	0[b] (None)	>0–0.99 (Light)	1–2.99 (Moderate)	≥3 (Heavy)
Proportion of participants, %	20.8	49.6	18.8	10.8	29.5	57.6	10.2	2.70
Alcohol use, g/day	0	4.0	22.6	96.6	0	2.7	21.1	77.9
Beer, drinks/day	0	0.11	0.56	3.29	0	0.03	0.20	1.33
Wine, drinks/day	0	0.10	0.56	0.62	0	0.10	0.78	0.85
Liquor, drinks/day	0	0.08	0.55	3.22	0	0.06	0.55	3.48
Smoking history								
Never smokers, %	35.6	33.3	25.2	16.1	55.3	45.0	29.2	19.5
Former smokers, %	52.7	55.5	63.1	62.2	30.8	39.2	48.3	42.4
Quit ≥10 years	40.9	44.7	51.6	47.5	21.1	27.8	34.5	26.9
Quit 5–9 years	7.6	6.9	7.7	9.4	5.9	7.0	8.7	9.4
Quit 2–4 years	4.2	3.9	3.8	5.3	3.8	4.4	5.1	6.1
Current smokers, %[c]	11.6	11.1	11.8	19.6	13.9	15.8	22.5	38.0
Age at entry of cohort, years	62	62	62	62	62	62	62	62
African American, %	4.0	2.5	1.8	2.1	8.5	4.5	2.4	4.4
Education, college or postcollege, %	35.3	45.8	52.7	44.6	23.2	31.8	38.3	32.1
Marital status, being married, %	84.3	86.3	85.2	81.1	43.3	44.7	47.6	42.0
Body mass index, kg/m^2	27.5	27.4	26.7	27.1	28.0	26.7	24.8	25.4
High-level physical activity, %[d]	48.8	49.6	54.6	47.6	39.8	42.7	47.8	38.0
Family history of first-degree cancer, %	46.2	47.5	48.1	47.4	50.9	51.7	52.4	50.8
Self-reported diabetes, %	17.1	9.8	5.5	6.1	14.1	4.9	2.1	2.6
Dietary intake per day[e]								
Total energy, kcal[f]	1,943	1,861	1,874	2,016	1,577	1,517	1,475	1,535
Total fat, g/1,000 kcal	35.4	34.7	32.9	27.8	33.9	33.6	32.0	27.3
Saturated fat, g/1,000 kcal	11.0	10.8	10.2	8.8	10.4	10.4	9.9	8.6
Red meat, g/1,000 kcal	38.0	38.4	38.0	35.9	29.1	30.0	30.1	29.1
Folate intake, mg/1,000 kcal	300	298	283	222	359	371	344	260

Abbreviation: NIH, National Institutes of Health.

[a] One drink was defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80 proof liquor, all equaling 13–14 g of alcohol.

[b] Nondrinkers.

[c] Included those who quit within 1 year.

[d] "High-level physical activity" was defined as activity that lasted at least 20 minutes and caused an increase in breathing or heart rate or worked up a sweat for at least 3–4 times per week.

[e] Dietary variables were adjusted for energy by using the density method.

[f] Excluding energy intake from alcoholic beverages.

Table 4 shows the associations between alcohol use and pancreatic cancer risk stratified by the number of years since quit smoking. Ever smokers drank more alcohol than never smokers did. Among never smokers and compared with respective light use, the relative risk for heavy total alcohol use and heavy liquor use increased nonsignificantly. We found a statistically significant increase in the risk of pancreatic cancer among longtime former smokers: Compared with that for light use, the relative risk for heavy total alcohol use was 1.41 (95% CI: 1.01, 2.00; $P_{trend} = 0.05$) in all participants. Similar patterns were seen in men and women (data not shown). Compared with that for light liquor use, the relative risk for heavy liquor use was 1.71 (95% CI: 1.12, 2.62; $P_{trend} = 0.02$) among longtime former smokers.

There were no statistically significant interactions of alcohol use on risk by lifelong smoking status ($P_{interaction} = 0.25$), the number of years since quit smoking ($P_{interaction} = 0.61$), folate intake ($P_{interaction} = 0.50$), or sex ($P_{interaction} = 0.95$). We evaluated the risk among participants with self-reported diabetes based on 161 cases and found that heavy total alcohol use was not associated with risk. The association of alcohol use with risk did not vary by diabetes status ($P_{interaction} = 0.30$). The significant associations between alcohol use and risk remained when we excluded

Table 2. Relative Risk of Pancreatic Cancer in Relation to Total Alcoholic Drinks per Day in the NIH-AARP Diet and Health Study, United States, 1995/1996–2003

Alcohol Use, drinks/day[a]	All						Men				Women[b]			
	Cases, no. (N = 1,149)	Person-Years, no.	Relative Risk[c]	95% Confidence Interval	Relative Risk[d]	95% Confidence Interval	Cases, no. (N = 748)	Person-Years, no.	Relative Risk[d]	95% Confidence Interval	Cases, no. (N = 401)	Person-Years, no.	Relative Risk[d]	95% Confidence Interval
Total alcohol														
0	305	826,749	1.16	1.01, 1.34	1.14	0.99, 1.32	168	416,263	1.12	0.93, 1.34	137	410,485	1.21	0.97, 1.51
>0–0.99	556	1,820,642	1.00	Referent	1.00	Referent	343	1,012,332	1.00	Referent	213	808,309	1.00	Referent
1–1.99	121	402,932	0.94	0.77, 1.14	0.92	0.75, 1.12	91	289,990	0.92	0.73, 1.16	30	112,943	0.90	0.61, 1.33
2–2.99	41	124,403	1.07	0.78, 1.47	1.03	0.75, 1.42	35	94,505	1.13	0.80, 1.61	6	29,898	0.69	0.30, 1.55
3–3.99	39	85,424	1.47	1.06, 2.04	1.31	0.94, 1.82	32	69,426	1.34	0.93, 1.94	15	37,251	1.24	0.72, 2.13
4–4.99	25	46,872	1.72	1.16, 2.58	1.54	1.02, 2.31	19	39,264	1.41	0.88, 2.26				
5–5.99	10	24,789	1.35	0.72, 2.52	1.28	0.68, 2.41	10	19,180	1.67	0.88, 3.15				
≥6	52	98,800	1.67	1.26, 2.22	1.55	1.13, 2.13	50	90,763	1.70	1.20, 2.38				
P_{trend}[e]				<0.001		0.004				0.001				0.79
1–2.99	162	527,337	0.97	0.81, 1.15	0.96	0.80, 1.15	126	384,495	0.97	0.79, 1.19	36	142,841	0.86	0.60, 1.23
≥3	126	255,885	1.59	1.31, 1.92	1.45	1.17, 1.80	111	218,634	1.50	1.18, 1.90	15	37,251	1.24	0.72, 2.13
P_{trend}[e]				<0.001		0.002				0.001				0.75

[a] One drink was defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80 proof liquor, all equal to 13–14 g of alcohol.

[b] For alcohol use among women, the highest category was ≥3 drinks/day.

[c] Relative risk was age adjusted. All Cox regression models were run with age as the underlying time metric.

[d] Relative risk was adjusted for sex (for all); smoking variable (never smokers, quit ≥10 years and smoked <20 cigarettes/day, quit ≥10 years and smoked ≥20 cigarettes/day, quit 5–9 years and smoked <20 cigarettes/day, quit 5–9 years and smoked ≥20 cigarettes/day, quit 1–4 years and smoked <20 cigarettes/day, quit 1–4 years and smoked ≥20 cigarettes/day, current smokers with <20 cigarettes/day, and current smokers with ≥20 cigarettes/day); total energy intake (continuous), energy-adjusted saturated fat, red meat, and total folate intake (continuous scale); body mass index (<20, 20–<25, 25–<30, ≥30 kg/m^2, missing); physical activity (low, moderate, and high level); and history of diabetes.

[e] The P value for linear trend was calculated by using the median values for each category as a single continuous variable.

Table 3. Relative Risk of Pancreatic Cancer in Relation to Alcoholic Drinks per Day According to Types of Beverages in the NIH-AARP Diet and Health Study, United States, 1995/1996–2003

Alcohol Use, drinks/day[a]	All				Men				Women			
	Cases, no. (N = 1,149)	Person-Years, no.	Relative Risk[b]	95% Confidence Interval	Cases, no. (N = 748)	Person-Years, no.	Relative Risk[b]	95% Confidence Interval	Cases, no. (N = 401)	Person-Years, no.	Relative Risk[b]	95% Confidence Interval
Beer												
0	546	1,565,850	1.17	1.01, 1.35	266	661,407	1.18	0.98, 1.42	280	904,442	1.16	0.92, 1.47
>0–0.99	518	1,626,827	1.00	Referent	400	1,151,633	1.00	Referent	118	475,194	1.00	Referent
≥1	85	237,935	1.07	0.84, 1.36	82	218,685	1.14	0.89, 1.46	3	19,250	0.53	0.17, 1.67
P_{trend}[c]			0.52				0.47				0.82	
Wine												
0	493	1,338,382	1.02	0.88, 1.17	391	1,094,166	0.93	0.78, 1.12	188	553,669	1.21	0.96, 1.53
>0–0.99	585	1,861,412	1.00	Referent	305	784,712	1.00	Referent	194	767,249	1.00	Referent
≥1	71	230,815	0.99	0.77, 1.26	52	152,846	0.99	0.74, 1.32	19	77,968	0.94	0.59, 1.52
P_{trend}[c]			0.72				0.58				0.78	
Liquor												
0	536	1,599,336	0.98	0.85, 1.14	318	868,214	0.99	0.82, 1.20	218	731,122	0.96	0.76, 1.22
>0–0.99	465	1,507,034	1.00	Referent	310	916,706	1.00	Referent	155	590,328	1.00	Referent
1–2.99	76	206,518	1.01	0.79, 1.29	60	152,997	1.03	0.78, 1.36	16	53,552	0.93	0.55, 1.56
≥3	72	117,723	1.62	1.24, 2.10	60	93,837	1.66	1.24, 2.23	12	23,886	1.46	0.80, 2.67
P_{trend}[c]			0.001				<0.001				0.25	

[a] One drink of beer, wine, or liquor is equal to 12.96 g, 13.72 g, or 13.93 g of alcohol, respectively (36).

[b] Relative risk was adjusted for sex (for all); smoking variable (never smokers, quit ≥10 years and smoked <20 cigarettes/day, quit ≥10 years and smoked ≥20 cigarettes/day, quit 5–9 years and smoked <20 cigarettes/day, quit 5–9 years and smoked ≥20 cigarettes/day, quit 1–4 years and smoked <20 cigarettes/day, quit 1–4 years and smoked ≥20 cigarettes/day, current smokers with <20 cigarettes/day, and current smokers with ≥20 cigarettes/day); total energy intake (continuous), energy-adjusted saturated fat, red meat, and total folate intake (continuous scale); body mass index (<20, 20–<25, 25–<30, ≥30 kg/m^2, missing); physical activity (low, moderate, and high level); history of diabetes; and use of other types of alcoholic beverages.

[c] The P value for linear trend was calculated by using the median values for each category as a single continuous variable.

the participants who were censored during the second year of follow-up.

DISCUSSION

In this NIH-AARP Diet and Health Study, we showed that heavy alcohol use (equivalent to ~40 g or 3 drinks daily), especially heavy liquor use, was associated with an increased risk of developing pancreatic cancer compared with light use. A significant positive association was observed for heavy liquor use among longtime former smokers. We observed a positive, albeit nonsignificant, association among never smokers.

Our findings of an increased risk of pancreatic cancer in heavy alcohol drinkers were in agreement with 5 case-control studies (18–22) and 3 cohort studies (7, 10, 17). Five studies have shown statistically significant relative risk ranging from 1.7 to 3.7 after adjustment for smoking (7, 10, 19, 20, 22). A moderately increased risk of pancreatic cancer was also observed in alcohol abusers compared with the general population (46, 47). In our study, the positive association was mostly explained by heavy liquor use. Heavy liquor use has been associated with pancreatic cancer in 3 North American studies (10, 17, 23). Volatile nitrosamines and polycyclic aromatic hydrocarbons are found in liquor and beer (48). Because nitrosamines are known pancreatic carcinogens in hamsters (49), the higher risk of pancreatic cancer could plausibly be explained by nitrosamines in liquor with heavy use (50). Alternatively, the positive association may be due to residual confounding by factors such as smoking and lifestyle factors. For example, we found that heavy liquor drinkers not only were more likely to be current smokers but also tended to have less total folate intake. Our study did not suggest an increased risk related to beer use or a decreased risk related to wine use as previously reported (10, 19–21, 23–27); however, we had few participants that were heavy beer or wine drinkers (≥3 drinks per day) and limited power to detect an association. Inconsistent findings on types of alcoholic beverage and pancreatic cancer risk may reflect different distributions of types of beverages consumed across different study populations. We may expect the association between alcohol use and pancreatic cancer to be confounded by other lifestyle behaviors if beverage preference differentially linked with such factors (51, 52). For example, a survey in 1995 revealed distinct drinking habits in the United States and Germany (53).

To minimize the residual confounding by smoking, we attempted to examine the association among never smokers. We found that heavy total alcohol or liquor use showed

Table 4. Relative Risk of Pancreatic Cancer in Relation to Alcoholic Drinks per Day According to the Number of Years Since Quit Smoking in the NIH-AARP Diet and Health Study, United States, 1995/1996–2003

Alcohol Use, drinks/day[a]	Never Smokers				Ever Smokers				Former Smokers Who Quit ≥10 Years Ago				Recent Quitters and Current Smokers			
	Median Drinks, no.	Cases, no. (N = 328)	Relative Risk[b]	95% Confidence Interval	Median Drinks, no.	Cases, no. (N = 821)	Relative Risk[c]	95% Confidence Interval	Cases, no. (N = 434)	Relative Risk[c]	95% Confidence Interval		Cases, no. (N = 387)	Relative Risk[c]	95% Confidence Interval	
Total alcohol																
0	0	99	0.98	0.76, 1.26	0	206	1.24	1.05, 1.48	99	1.13	0.89, 1.44		107	1.37	1.07, 1.74	
>0–0.99	0.12	177	1.00	Referent	0.16	379	1.00	Referent	210	1.00	Referent		169	1.00	Referent	
1–2.99	1.49	36	0.94	0.66, 1.36	1.61	126	0.95	0.78, 1.17	77	1.01	0.78, 1.32		68	0.87	0.63, 1.20	
≥3	6.13	16	1.35	0.79, 2.30	6.27	110	1.50	1.18, 1.90	48	1.41	1.01, 2.00		43	1.54	1.11, 2.13	
P_{trend}[d]				0.41				0.003			0.05				0.09	
Liquor[e]																
0	0	164	0.81	0.62, 1.07	0	372	1.07	0.90, 1.27	194	1.02	0.80, 1.29		178	1.13	0.88, 1.45	
>0–0.99	0.05	144	1.00	Referent	0.05	321	1.00	Referent	178	1.00	Referent		143	1.00	Referent	
1–2.99	1.37	12	0.86	0.47, 1.55	1.37	64	1.07	0.82, 1.40	35	1.14	0.79, 1.64		29	1.00	0.67, 1.49	
≥3	4.49	8	1.43	0.69, 2.96	4.91	64	1.73	1.30, 2.29	27	1.71	1.12, 2.62		37	1.66	1.13, 2.43	
P_{trend}[d]				0.37				<0.001			0.02				0.02	

[a] One drink was defined as 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80 proof liquor, all equal to 13–14 g of alcohol.
[b] Relative risk was adjusted for sex (for all); total energy intake, energy-adjusted saturated fat, red meat, and total folate intake (continuous scale); body mass index (<20, 20–<25, 25–<30, ≥30 kg/m^2, missing); physical activity (low, moderate, and high level); and history of diabetes.
[c] In smokers, relative risk was additionally adjusted for smoking dose and smoking duration.
[d] The P value for linear trend was calculated by using the median values for each category as a single continuous variable.
[e] Multiple covariate-adjusted models additionally included use of other types of alcoholic beverages.

a slightly increased risk of developing pancreatic cancer in never smokers. Although the association was not statistically significant, the magnitude of the association was similar to that of ever smokers, and there was no significant interaction across various smoking statuses. This observation was consistent with the results from 2 North American studies (17, 21) that suggested that heavy alcohol use was an independent etiologic component for pancreatic cancer. However, our study was limited by the fact that only 16 cases arose among 5,870 participants who were never-smoking heavy drinkers.

Notably, we found a significantly increased risk of pancreatic cancer associated with heavy total alcohol and liquor use among longtime former smokers. In our study, 38% of participants were former smokers who had quit smoking 10 or more years ago before baseline, and these participants, in particular men, did not have a significant, higher risk of developing pancreatic cancer compared with never smokers. Although we could not completely exclude residual confounding by cigarette smoking, the significant positive association between alcohol use and pancreatic cancer in longtime former smokers might suggest a potential etiologic role of alcohol use in pancreatic cancer development.

The mechanisms by which heavy alcohol use may increase human pancreatic cancer risk have not been well elucidated (54). Animal studies have shown that the pancreas can metabolize ethanol by means of oxidative and nonoxidative pathways (55). The metabolites of the oxidative pathway, acetaldehyde and reactive oxygen species, could injure pancreatic tissues and alter the pathways involved in the inflammatory response and carcinogenesis (56–58). The metabolites of the nonoxidative pathway, fatty acid ethyl esters, could induce pancreatic injury in male rats (59). Recently, Gukovsky et al. (60) developed a rat model of alcohol-mediated postacute pancreatitis that produced the 3 key pathologic responses of human alcoholic chronic pancreatitis, including loss of parenchyma, sustained inflammation, and fibrosis. A prevailing opinion is that alcohol consumption sensitizes the pancreas to inflammatory, immune, and fibrosing responses induced by genetic and environmental predisposing factors (61–63) and functions as a cofactor in the development of pancreatic disease. It is unknown whether heavy alcohol use would cause the aforementioned changes in the human pancreas and predispose the pancreas to inflammatory response and carcinogenesis. Because we did not collect information on pancreatitis or other pancreatic diseases, we could not test the hypothesis that pancreatitis is one of the mechanisms that explains the association between heavy alcohol use and pancreatic cancer.

The strengths of our prospective study include its considerable sample size and wide range of alcohol consumption. The NIH-AARP Diet and Health Study cohort of older individuals provided an appropriate population for the study of pancreatic cancer that may be generalizable to other older populations. Differential recall bias was precluded because information on exposure was collected before diagnosis of pancreatic cancer. Given the large number of cases, we had an adequate sample size to estimate the risk in heavy drinkers overall. We were able to examine the association

in long-term former smokers who were no longer at a higher risk of developing pancreatic cancer due to cigarette smoking. However, we did not have an adequate number of cases among women and never smokers or among heavy beer or wine drinkers to observe a statistically significant association with pancreatic cancer risk. In addition, we may not have captured the etiologically relevant window of exposure using baseline exposure assessment. Along the same lines, we did not collect information on duration of alcohol use. It has been suggested that long periods of time may exert a measurable risk of pancreatic cancer (2). Finally, because the majority of participants were non-Hispanic white, the study did not have enough power to examine the association among other ethnic groups.

In summary, we confirmed previous findings that moderate alcohol use was not a risk factor for pancreatic cancer. Our findings suggested that heavy alcohol use, especially heavy liquor use, may play a role in pancreatic cancer etiology, although we could not completely exclude residual confounding by smoking. We hope our study would stimulate more studies to address the residual confounding of smoking in the relation between alcohol use and risk of pancreatic cancer.

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REFERENCES

1. World Cancer Research Fund/American Institute for Cancer Research. Alcoholic drinks. In: *Food, Nutrition, Physical Activity, and Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 2007:157–171.
2. Velema JP, Walker AM, Gold EB. Alcohol and pancreatic cancer: insufficient epidemiologic evidence for a causal relationship. *Epidemiol Rev.* 1986;8(1):28–41.
3. Anderson K, Mack T, Silverman D. Cancer of the pancreas. In: Schottenfeld D, Fraumeni J, eds. *Cancer Epidemiology and Prevention*. New York, NY: Oxford University Press; 2006: 741–742.
4. Friedman GD, van den Eeden SK. Risk factors for pancreatic cancer: an exploratory study. *Int J Epidemiol*. 1993;22(1):30–37.
5. Hakulinen T, Lehtimaki L, Lehtonen M, et al. Cancer morbidity among two male cohorts with increased alcohol consumption in Finland. *J Natl Cancer Inst*. 1974;52(6):1711–1714.
6. Jensen OM. Cancer morbidity and causes of death among Danish brewery workers. *Int J Cancer.* 1979;23(4):454–463.
7. Heuch I, Kvåle G, Jacobsen BK, et al. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. *Br J Cancer.* 1983; 48(5):637–643.
8. Hiatt RA, Klatsky AL, Armstrong MA. Pancreatic cancer, blood glucose and beverage consumption. *Int J Cancer.* 1988; 41(6):794–797.
9. Hirayama T. Epidemiology of pancreatic cancer in Japan. *Jpn J Clin Oncol*. 1989;19(3):208–215.
10. Zheng W, McLaughlin JK, Gridley G, et al. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). *Cancer Causes Control*. 1993; 4(5):477–482.
11. Shibata A, Mack TM, Paganini-Hill A, et al. A prospective study of pancreatic cancer in the elderly. *Int J Cancer.* 1994; 58(1):46–49.
12. Coughlin SS, Calle EE, Patel AV, et al. Predictors of pancreatic cancer mortality among a large cohort of United States adults. *Cancer Causes Control*. 2000;11(10):915–923.
13. Stolzenberg-Solomon RZ, Pietinen P, Barrett MJ, et al. Dietary and other methyl-group availability factors and pancreatic cancer risk in a cohort of male smokers. *Am J Epidemiol*. 2001; 153(7):680–687.
14. Michaud DS, Giovannucci E, Willett WC, et al. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol Biomarkers Prev.* 2001;10(5):429–437.
15. Lin Y, Tamakoshi A, Kawamura T, et al. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan Collaborative Cohort Study for Evaluation of Cancer Risk. *Int J Cancer.* 2002;99(5): 742–746.
16. Isaksson B, Jonsson F, Pedersen NL, et al. Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer.* 2002;98(3):480–482.
17. Harnack LJ, Anderson KE, Zheng W, et al. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev.* 1997;6(12):1081–1086.
18. Durbec JP, Chevillotte G, Bidart JM, et al. Diet, alcohol, tobacco and risk of cancer of the pancreas: a case-control study. *Br J Cancer.* 1983;47(4):463–470.
19. Olsen GW, Mandel JS, Gibson RW, et al. A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health*. 1989;79(8):1016–1019.
20. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int J Cancer.* 1989;43(3): 415–421.
21. Silverman DT, Brown LM, Hoover RN, et al. Alcohol and pancreatic cancer in blacks and whites in the United States. *Cancer Res.* 1995;55(21):4899–4905.
22. Lu XH, Wang L, Li H, et al. Establishment of risk model for pancreatic cancer in Chinese Han population. *World J Gastroenterol*. 2006;12(14):2229–2234.
23. Villeneuve PJ, Johnson KC, Hanley AJ, et al. Alcohol, tobacco and coffee consumption and the risk of pancreatic cancer: results from the Canadian Enhanced Surveillance System

case-control project. Canadian Cancer Registries Epidemiology Research Group. *Eur J Cancer Prev.* 2000;9(1):49–58.
24. Mack TM, Yu MC, Hanisch R, et al. Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst*. 1986;76(1):49–60.
25. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, et al. Lifetime consumption of alcoholic beverages, tea and coffee and exocrine carcinoma of the pancreas: a population-based case-control study in the Netherlands. *Int J Cancer.* 1992; 50(4):514–522.
26. Gold EB, Gordis L, Diener MD, et al. Diet and other risk factors for cancer of the pancreas. *Cancer.* 1985;55(2):460–467.
27. Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int J Cancer.* 1990;45(5):816–820.
28. Schneider A, Singer MV. Alcoholic pancreatitis. *Dig Dis*. 2005; 23(3–4):222–231.
29. Kristiansen L, Gronbaek M, Becker U, et al. Risk of pancreatitis according to alcohol drinking habits: a population-based cohort study. *Am J Epidemiol*. 2008;168(8):932–937.
30. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med*. 1993;328(20):1433–1437.
31. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol*. 2001;154(12):1119–1125.
32. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Regist Manage*. 2005;32(2):70–75.
33. Fritz A, Percy C, Jack A, et al. *International Classification of Diseases for Oncology (ICD-O)*. 3rd ed. Geneva, Switzerland: World Health Organization; 2000.
34. Subar AF, Midthune D, Kulldorff M, et al. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. *Am J Epidemiol*. 2000;152(3): 279–286.
35. Thompson FE, Kipnis V, Midthune D, et al. Performance of a food-frequency questionnaire in the US NIH-AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. *Public Health Nutr.* 2008; 11(2):183–195.
36. Friday J, Bowman S. *MyPyramid Equivalent Database for USDA Survey Food Codes, 1994–2002, Version 1.0*. Beltsville, MD: USDA; Agriculture Research Service; 2006.
37. Millen AE, Midthune D, Thompson FE, et al. The National Cancer Institute diet history questionnaire: validation of pyramid food servings. *Am J Epidemiol*. 2006;163(3):279–288.
38. Cox DR. Regression models and life tables. *J R Stat Soc (B).* 1972;34:187–202.
39. Thiebaut AC, Benichou J. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. *Stat Med.* 2004;23(24):3803–3820.
40. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3): 515–526.
41. Shaper AG, Wannamethee G, Walker M. Alcohol and mortality in British men: explaining the U-shaped curve. *Lancet*. 1988;2(8623):1267–1273.
42. Ji BT, Chow WH, Dai Q, et al. Cigarette smoking and alcohol consumption and the risk of pancreatic cancer: a case-control study in Shanghai, China. *Cancer Causes Control*. 1995;6(4): 369–376.
43. Norell SE, Ahlbom A, Erwald R, et al. Diet and pancreatic cancer: a case-control study. *Am J Epidemiol*. 1986;124(6): 894–902.
44. Boyle P, Maisonneuve P, Bueno de Mesquita B, et al. Cigarette smoking and pancreas cancer: a case control study of the search programme of the IARC. *Int J Cancer.* 1996;67(1):63–71.
45. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med*. 1996;156(19):2255–2260.
46. Adami HO, McLaughlin JK, Hsing AW, et al. Alcoholism and cancer risk: a population-based cohort study. *Cancer Causes Control*. 1992;3(5):419–425.
47. Tonnesen H, Moller H, Andersen JR, et al. Cancer morbidity in alcohol abusers. *Br J Cancer.* 1994;69(2):327–332.
48. Walker EA, Castegnaro M, Garren L, et al. Intake of volatile nitrosamines from consumption of alcohols. *J Natl Cancer Inst*. 1979;63(4):947–951.
49. Hall PA, Lemoine NR. Models of pancreatic cancer. *Cancer Surv.* 1993;16:135–155.
50. Raymond L, Infante F, Tuyns AJ, et al. Diet and cancer of the pancreas. (In French). *Gastroenterol Clin Biol.* 1987;11(6-7): 488–492.
51. Bloomfield K, Stockwell T, Gmel G, et al. International comparisons of alcohol consumption. *Alcohol Res Health*. 2003;27(1):95–109.
52. Della Valle E, Stranges S, Trevisan M, et al. Drinking habits and health in northern Italian and American men. *Nutr Metab Cardiovasc Dis*. 2009;19(2):115–122.
53. Bloomfield K, Greenfield TK, Kraus L, et al. A comparison of drinking patterns and alcohol-use-related problems in the United States and Germany, 1995. *Subst Use Misuse*. 2002; 37(4):399–428.
54. Go VL, Gukovskaya A, Pandol SJ. Alcohol and pancreatic cancer. *Alcohol*. 2005;35(3):205–211.
55. Laposata EA, Lange LG. Presence of nonoxidative ethanol metabolism in human organs commonly damaged by ethanol abuse. *Science*. 1986;231(4737):497–499.
56. Apte MV, Pirola RC, Wilson JS. Battle-scarred pancreas: role of alcohol and pancreatic stellate cells in pancreatic fibrosis. *J Gastroenterol Hepatol*. 2006;21(suppl 3):S97–S101.
57. Altomare E, Grattagliano I, Vendemiale G, et al. Acute ethanol administration induces oxidative changes in rat pancreatic tissue. *Gut*. 1996;38(5):742–746.
58. Pandol SJ, Periskic S, Gukovsky I, et al. Ethanol diet increases the sensitivity of rats to pancreatitis induced by cholecystokinin octapeptide. *Gastroenterology.* 1999;117(3):706–716.
59. Werner J, Saghir M, Warshaw AL, et al. Alcoholic pancreatitis in rats: injury from nonoxidative metabolites of ethanol. *Am J Physiol Gastrointest Liver Physiol*. 2002;283(1):G65–G73.
60. Gukovsky I, Lugea A, Shahsahebi M, et al. A rat model reproducing key pathological responses of alcoholic chronic pancreatitis. *Am J Physiol Gastrointest Liver Physiol*. 2008; 294(1):G68–G79.
61. Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. *Gut*. 1999;45(3):317–322.
62. Jerrells TR, Chapman N, Clemens DL. Animal model of alcoholic pancreatitis: role of viral infections. *Pancreas*. 2003; 27(4):301–304.
63. Oruc N, Whitcomb DC. Theories, mechanisms, and models of alcoholic chronic pancreatitis. *Gastroenterol Clin North Am.* 2004;33(4):733–750, v–vi.