Alcohol Intake and Pancreatic Cancer Risk: A Pooled Analysis of Fourteen Cohort Studies

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Abstract

Background: Few risk factors have been implicated in pancreatic cancer etiology. Alcohol has been theorized to promote carcinogenesis. However, epidemiologic studies have reported inconsistent results relating alcohol intake to pancreatic cancer risk.
Methods: We conducted a pooled analysis of the primary data from 14 prospective cohort studies. The study sample consisted of 862,664 individuals among whom 2,187 incident pancreatic cancer cases were identified. Study-specific relative risks and 95% confidence intervals were calculated using Cox proportional hazards models and then pooled using a random effects model.
Results: A slight positive association with pancreatic cancer risk was observed for alcohol intake (pooled multivariate relative risk, 1.22; 95% confidence interval, 1.03-1.45 comparing ≥30 to 0 grams/day of alcohol; P value, test for between-studies heterogeneity = 0.80).

For this comparison, the positive association was only statistically significant among women although the difference in the results by gender was not statistically significant (P value, test for interaction = 0.19). Slightly stronger results for alcohol intake were observed when we limited the analysis to cases with adenocarcinomas of the pancreas. No statistically significant associations were observed for alcohol from wine, beer, and spirits comparing intakes of ≥5 to 0 grams/day. A stronger positive association between alcohol consumption and pancreatic cancer risk was observed among normal weight individuals compared with overweight and obese individuals (P value, test for interaction = 0.01).
Discussion: Our findings are consistent with a modest increase in risk of pancreatic cancer with consumption of 30 or more grams of alcohol per day. (Cancer Epidemiol Biomarkers Prev 2009;18(3):765–76)

Background

Worldwide, pancreatic cancer is the 13th and 12th most common cause of cancer and the 7th and 9th most common cause of cancer mortality in males and females, respectively (1). Given that pancreatic cancer has few early symptoms, it is most often diagnosed at late stages and has an extremely low 5-year survival rate (<5%; ref. 2). Few risk factors for pancreatic cancer are well established or widely accepted. Due to the current lack of good screening methods for pancreatic cancer and low survival rates, a better understanding of the etiology of cancer may lead to means to reduce pancreatic cancer incidence.

Heavy alcohol drinking has been positively associated with risk of chronic pancreatitis (3, 4) and noninsulin-dependent diabetes mellitus (5), two diseases that have been associated with an increased risk of pancreatic cancer (6-10). Thus, high alcohol intake has been hypothesized to be associated with a higher risk of pancreatic cancer. There are several biological mechanisms by which alcohol has been theorized to promote carcinogenesis: (*a*) through the oxidation byproduct of alcohol metabolism, acetaldehyde, which may act as a cocarcinogen; (*b*) through up-regulation of immunosuppressive and inflammatory pathways; (*c*) by induction of Phase I cytochrome P450 biotransformation enzymes that are involved in the activation of carcinogens in the liver and other tissues; and (*e*)by depletion of folate, which may alter DNA synthesis and transcription (11-14).

Most (15-34), but not all (29, 35-44), case-control studies of pancreatic cancer have observed no association with alcohol intake. Additionally, inconsistent associations have been reported with pancreatic cancer risk from 12 prospective studies (45-56), which included four of the studies in this pooled analysis, the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (54), Health Professionals Follow-up Study (52), Iowa Women's Health Study (46), and the Nurses' Health Study (52). In 2007, a panel sponsored by the World Cancer Research Fund and American Institute of Cancer Research concluded that the current data on the relationship between alcohol intake and pancreatic cancer risk were too inconsistent to reach a judgment on the association between alcohol intake and risk of cancer of the pancreas (57).

Due to the potential for recall bias in case-control studies and the limited power of most cohort studies to examine associations with pancreatic cancer, we investigated the association between alcohol intake and pancreatic cancer risk in a pooled analysis of 14 prospective studies. Because the effect of alcohol may vary by potential pancreatic cancer risk factors, we also considered whether the association differed by environmental and nutritional factors. In addition, individual histologic subtypes of pancreatic cancer may be associated with different etiologies. Thus, we examined associations between intakes of alcohol separately for adenocarcinomas of the pancreas, the predominant type of pancreatic cancer (58-62).

Materials and Methods

Population. A pooled analysis of the primary data from 14 prospective cohort studies (46, 52, 63-72) was conducted in The Pooling Project of Prospective Studies of Diet and Cancer (Table 1). To be included in this analysis, each study needed to fulfill the following prespecified inclusion criteria: a minimum of 50 incident pancreatic cancer cases, an assessment of usual diet, including alcohol intake, validation of the dietary assessment tool or a closely related instrument, and a publication of a diet and cancer association.

The methods for the Pooling Project have been described in detail elsewhere (73). Studies including both men and women were treated as two separate cohorts (one of men and one of women), analyzed separately, and the inclusion criteria were applied to each gender-specific cohort. Two studies in the pooled analysis, the Canadian National Breast Screening Study and Netherlands Cohort Study, were analyzed as case-cohort studies (66, 69). In addition, we have divided the person-time of the Nurses' Health Study into two segments corresponding to the 1980 to 1986 follow-up period (part a) and follow-up beginning in 1986 (part b) to take advantage of the increased comprehensiveness of the 131-item food-frequency questionnaire (FFQ) completed in 1986 compared with the 61-item FFQ completed in 1980. In the pancreatic cancer analyses, we only used data from the Nurses' Health Study (part b) because fewer than 50 cases were identified between 1980 and 1986. For the Swedish Mammography Cohort, we used 1997 as the baseline (questionnaire and follow-up) because the 1997 questionnaire included information on smoking habits, an important risk factor for pancreatic cancer; only cases diagnosed from 1997 forward were included in our analysis.

Exclusion. In addition to applying the exclusions that each study had predefined for their cohort, we excluded individuals if they had a prior cancer diagnosis other than nonmelanoma skin cancer at baseline, had log_e-transformed energy intakes beyond three SDs of the study- and sex-specific log_e-transformed mean energy intake of their respective population, or were missing data on alcohol intake.

Exposure Assessment. Usual dietary intake was estimated at baseline from study-specific FFQs. All studies, except the New York State Cohort, measured alcohol intake from wine, beer, and spirits separately (see Table 1). Each of these studies calculated daily alcohol intake in grams for each beverage based on the reported frequency of consumption, the alcohol content of the beverage, and the average quantity consumed. As an example, the US Department of Agriculture conversion factors[22] for alcoholic beverages are 12.8 grams (335 mL) of alcohol for a 12-oz can or bottle of beer, 11.0 grams for a 4-oz (118 mL) glass of wine, and 14.0 grams for 1.5 oz (44 mL) of 80-proof liquor. The alcohol intake from each specific beverage was summed to estimate total alcohol intake. Intakes of other nutrients were estimated using a similar approach. In the New York State Cohort, the ''regression weight'' method was used to estimate nutrient and alcohol values (63). Correlations between energy-adjusted alcohol intake measured from the study-specific FFQ or a closely related instrument and multiple 24-h recalls or food records generally exceeded 0.7 for total alcohol intake (74-82).[23]

Information on nondietary factors was collected on the baseline self-administered questionnaires within each study. All studies obtained information on height and weight, whereas 11 of the studies ascertained diabetes status. Smoking status (never, former, or current smoker) was ascertained in all studies. By design, the α-Tocopherol β-Carotene Cancer Prevention Study included only men who were current smokers (72). Smoking habits (e.g., duration of smoking and number of cigarettes smoked at baseline) were ascertained in all studies, except The New York State Cohort (63), which

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[22] http://www.nal.usda.gov/fnic/foodcomp
[23] Wolk et al., personal communication.

Table 1. Daily median intakes (interquartile range) of alcohol (grams/d) among drinkers by cohort study in the pancreatic cancer analyses in the Pooling Project of Prospective Studies of Diet and Cancer

Cohort*	Gender	Follow-up years	Baseline cohort size[†]	No. cases	Age (y)	% of alcohol drinkers[‡]	Median (IQR) alcohol intake (grams/d)[§] among drinkers of that beverage			
							Total alcohol intake	Alcohol from wine intake	Alcohol from beer intake	Alcohol from liquor intake
ATBC	Male	1984-1999	26,987	204	50-69	89	13.4 (5.3-27.7)	2.1 (0.7-4.6)	4.6 (1.7-11.6)	8.0 (1.8-21.3)
BCDDP	Female	1987-1999	43,162	102	40-93	51	3.1 (0.9-10.3)	1.4 (0.4-4.6)	0.9 (0.3-1.9)	2.2 (0.5-6.5)
CNBSS‖	Female	1980-2000	49,654	105	40-59	77	6.2 (2.3-14.5)	3.1 (1.0-6.7)	1.7 (0.9-3.7)	2.3 (1.1-6.8)
CPS II	Female	1992-2001	74,138	164	50-74	52	4.3 (1.1-11.1)	1.4 (0.7-5.8)	0.9 (0.9-2.8)	2.1 (0.9-11.0)
	Male	1992-2001	66,165	210	50-74	65	9.6 (2.7-21.3)	1.9 (0.9-5.8)	1.9 (0.9-7.3)	7.0 (1.1-16.4)
CTS	Female	1995-2001	100,030	116	22-104	67	7.8 (4.0-13.2)	3.3 (3.3-11.1)	4.0 (4.0-4.0)	4.5 (4.5- 4.5)
COSM	Male	1998-2004	45,338	75	45-79	92	9.0 (4.3-15.5)	2.4 (0.6-6.2)	5.0 (2.3-9.6)	1.8 (0.4-4.4)
HPFS	Male	1986-2002	47,762	198	40-75	76	9.6 (3.8-18.1)	1.8 (1.5-5.6)	1.8 (1.0-5.5)	6.0 (1.1-11.2)
IWHS	Female	1986-2001	34,588	171	55-69	45	3.4 (1.7-10.8)	1.7 (0.9-3.0)	1.9 (1.1-5.7)	2.1 (1.2-6.5)
MCCS	Female	1991-2003	22,830	35	40-69	59	8.6 (2.1-16.4)	6.4 (2.0-15.0)	0.9 (0.2-3.0)	1.3 (0.3-2.7)
	Male	1991-2003	14,908	28	40-69	83	17.3 (6.7-34.0)	10.7 (3.0-25.7)	4.0 (1.4-13.9)	1.4 (0.3-4.1)
NLCS‖	Female	1986-1995	62,573	115	55-69	68	4.3 (1.5-12.0)	3.5 (1.3-9.7)	1.1 (0.4-2.3)	3.7 (1.1-12.1)
	Male	1986-1995	58,279	144	55-69	86	12.5 (5.1-25.0)	3.9 (1.4-10.3)	2.3 (1.1-7.4)	9.3 (2.1-16.7)
NYSC	Female	1980-1987	22,550	48	15-107	78	1.9 (0.5-9.5)	(−)	(−)	(−)
	Male	1980-1987	30,363	90	15-107	89	4.8 (1.0-19.0)	(−)	(−)	(−)
NHS	Female	1986-2002	68,478	178	40-65	64	4.7 (1.8-12.3)	1.8 (0.9-5.6)	1.8 (1.0-5.5)	2.0 (1.1-6.0)
PLCO	Female	1993-2004	28,315	60	55-74	73	1.6 (0.4-8.5)	0.4 (0.3-2.4)	0.2 (0.1-1.0)	0.3 (0.2-2.7)
	Male	1993-2004	29,914	90	55-74	82	7.9 (1.4-24.5)	0.3 (0.3-2.5)	1.1 (0.3-7.2)	1.4 (0.4-9.1)
SMC	Female	1997-2003	36,630	54	49-83	83	3.1 (1.2-6.3)	2.0 (0.4-4.5)	1.3 (0.4-2.8)	0.2 (0.2-1.1)

Abbreviation: IQR, interquartile range.

*ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; CNBSS, Canadian National Breast Screening Study; CPS II, Cancer Prevention Study II Nutrition Cohort; CTS, California Teachers Study; COSM, Cohort of Swedish Men; HPFS, Health Professionals Follow-up Study; IWHS, Iowa Women's Health Study; MCCS, Melbourne Collaborative Cohort Study; NLCS, The Netherlands Cohort Study; NYSC, New York State Cohort; NHS, Nurses' Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort.

[†] Baseline cohort size and number of cases determined after applying study-specific exclusion criteria and excluding participants with prior cancer diagnosis other than nonmelanoma skin cancer at baseline, missing alcohol intake and log_e-transformed energy intake beyond three SDs from the study-specific log_e-transformed mean energy intake of the population.

[‡] Percentage of alcohol drinkers at baseline for each cohort study.

[§] Median intakes are grams/d for alcohol and alcohol from specific beverages among drinkers of that beverage.

‖ Canadian National Breast Screening Study and Netherlands Cohort Study are analyzed as case-cohort studies so the baseline cohort size does not reflect the above exclusions.

ascertained the usual number of cigarettes smoked daily and duration of smoking.

Outcome Assessment. Invasive pancreatic cancer, defined by International Classification of Diseases 9 code 157.0 (83) or International Classification of Diseases 10 code C25 (84), was ascertained by self-report with subsequent medical record review (52), cancer registry linkage (46, 63, 65, 66, 68, 69, 71), or both (64, 67, 70, 72). Some studies additionally obtained information from death registries (46, 52, 63-65, 67, 70). Of the 2,187 invasive pancreatic cancer cases identified, the majority were classified as adenocarcinomas (n = 1,491 cases) using International Classification of Diseases-O codes 8140-8149, 8160-8169, 8180-8229, 8250-8509, 8520-8560, and 8570-8579 in those studies that had information on histologic detail.

Statistical Analysis. Alcohol intake was modeled categorically within each individual study using identical absolute cutpoints (none, 0.1-4.9, 5.0-14.9, 15.0-29.9, and ≥30 grams/d) based on multiples of 1 drink per day (~ 15 grams/d). Alcohol consumption was higher among the men, so in a subanalysis among the men, we expanded the ≥30 grams/d category to three categories (30-44.9, 45-59.9, and ≥60 grams/d). When examining alcohol intake from specific beverages, studies were excluded from the analysis if they did not measure intake of that specific beverage. Due to the small number of cases at higher intakes, the categories for alcohol intake from specific beverages were less extreme than those for total alcohol intake. Alcohol intake from specific beverages was modeled categorically within each individual study using identical absolute cutpoints (none, 0.1-4.9, and ≥5 grams/d). Additional subanalyses were conducted to examine a larger contrast in intake of alcohol from beer and spirits among men using the following cutpoints (none, 0.1-4.9, 5-14.9, and ≥15 grams/d).

Relative risks (RR) and 95% confidence intervals (CI) were calculated by Cox proportional hazards models (85) for each study. Person-years of follow-up were calculated from the date of the baseline questionnaire until date of pancreatic cancer diagnosis, date of death, date the participant moved out of the study area (if applicable), or end of follow-up, whichever came first. The models included stratification by age (years) at baseline and the calendar year at start of follow-up, and treated follow-up time (days) as the time scale. Multivariate RRs were adjusted for smoking status (never smoker; past smokers, pack-years of <15 y; past smoker, pack-years of ≥15 y; current smokers, pack-years of <40 y; current smokers, pack-years of ≥40 y), personal history of diabetes (no, yes), body mass index (BMI; continuously), and energy intake (continuously). As personal history of diabetes may be in the causal pathway (or an intermediate variable), we conducted the analysis of alcohol intake and pancreatic cancer risk removing the covariate personal history of diabetes from the model. An indicator variable for missing values was also generated within a study for each covariate, if applicable (73). If no participants diagnosed with pancreatic cancer were in the highest intake category in a study, the RR for the highest category could not be estimated in that study and the noncases in the highest category in that study were included in the second highest intake category.

To test whether there was a linear trend in the risk of pancreatic cancer with increasing alcohol intake, a continuous variable with values corresponding to the median value for each exposure category was included in the model; the statistical significance of the coefficient for that variable was evaluated using the Wald test.

Study-specific RRs were pooled using a random effects model (86). The study-specific RRs were weighted by the inverse of the sum of their variance and the estimated between-studies variance component. Between-studies heterogeneity was evaluated using the Q statistic (86, 87).

We also evaluated whether total alcohol intake and alcohol intakes from wine, beer, and spirits were linearly associated with pancreatic cancer risk. To test for nonlinearity, the model fit including the linear and cubic spline terms selected by a stepwise regression procedure was compared with the model fit with only the linear term using the likelihood ratio test (88, 89). For these analyses, the studies were combined into a single data set, additionally stratified by study, age, and the year the questionnaire was returned. The estimate was additionally adjusted for smoking status, diabetes, BMI, and energy intake. Due to the small numbers of individuals consuming high amounts of alcohol and to avoid excess influence of extreme intake, these analyses were limited to individuals consuming <60 grams/d of alcohol [59 cases (or <3%) were excluded]. For each study, we corrected the RR for total alcohol intake for measurement error using the regression coefficients between alcohol intakes estimated by the FFQs and reference methods (90, 91).

In additional analyses, we examined the effect of different parameterizations of smoking variables on the risk estimates observed for alcohol intake. We conducted separate analyses in which we adjusted for smoking history using the following categorizations: (*a*) smoking status only (never, past, current); (*b*) smoking status and smoking duration; (*c*) smoking status and smoking dose; (*d*) smoking status, smoking duration among past smokers, and smoking dose among current smokers; and (*e*) smoking status and smoking pack-years to replace the categorization we used for the main multivariate models.

Further analyses were conducted to examine whether the association between alcohol consumption and pancreatic cancer risk varied by life-style and nutritional factors. To evaluate whether the association between alcohol consumption and pancreatic cancer risk varied by gender and smoking status, which can only be evaluated between-studies or as a nominal variable, respectively, we used a meta-regression model (92). To examine for variation in RRs by BMI, multivitamin use, methionine intake, and combined dietary and supplemental folate intake, we first calculated pooled RRs for alcohol consumption and the potential effect modifier modeled as continuous variables, and then assessed the statistical significance of the cross-product term between alcohol consumption and the potential effect modifier using a Wald test. A two-sided Wald test statistic was used to test the null hypothesis that there was no modification of the alcohol-pancreatic cancer association by levels of the potential effect modifiers. Participants with missing values of the modifying factor were excluded from these analyses. Separate analyses were also conducted for the adenocarcinoma subtype among those studies having >10 cases of this specific subtype

Table 2. Study-specific multivariate adjusted RRs and 95% CIs and pooled age and multivariate adjusted RRs and 95% CIs for pancreatic cancer according to intake of total alcohol

Study	Gender	RR (95% CI)	Categories of alcohol intake (grams/d)					P-value, test for between-studies heterogeneity*	P-value, test for between-studies heterogeneity due to sex[†]	P-value, test for trend[‡]
			0	0.1-4.9	5-14.9	15-29.9	≥30			
ATBC	Male	MV RR	1.00	1.04	1.00	0.82	0.99			0.67
		95% CI	(Reference)	(0.64-1.69)	(0.63-1.61)	(0.49-1.37)	(0.59-1.67)			
BCDDP	Female	MV RR	1.00	1.29	0.84	0.81	1.71			0.75
		95% CI	(Reference)	(0.82-2.02)	(0.42-1.70)	(0.32-2.08)	(0.65-4.50)			
CNBSS	Female	MV RR	1.00	0.94	0.82	0.76	1.14			0.89
		95% CI	(Reference)	(0.56-1.56)	(0.47-1.43)	(0.35-1.65)	(0.56-2.33)			
CPS II	Female	MV RR	1.00	0.85	0.80	1.16	0.87			0.91
		95% CI	(Reference)	(0.58-1.24)	(0.49-1.29)	(0.57-2.34)	(0.37-2.06)			
	Male	MV RR	1.00	1.01	1.23	1.11	1.41			0.12
		95% CI	(Reference)	(0.69-1.50)	(0.84-1.79)	(0.69-1.80)	(0.91-2.20)			
CTS	Female	MV RR	1.00	1.02	0.81	1.23	1.31			0.35
		95% CI	(Reference)	(0.60-1.72)	(0.49-1.36)	(0.71-2.12)	(0.59-2.90)			
COSM	Male	MV RR	1.00	1.07	1.30	0.97	1.79			0.48
		95% CI	(Reference)	(0.45-2.56)	(0.56-3.00)	(0.37-2.55)	(0.58-5.49)			
HPFS	Male	MV RR	1.00	0.95	0.78	0.68	0.74			0.16
		95% CI	(Reference)	(0.64-1.40)	(0.53-1.16)	(0.41-1.14)	(0.45-1.21)			
IWHS	Female	MV RR	1.00	1.26	1.04	1.97	1.20			0.37
		95% CI	(Reference)	(0.88-1.80)	(0.62-1.76)	(1.06-3.67)	(0.54-2.69)			
MCCS	Female	MV RR	1.00	0.80	0.18	0.75	1.57			0.78
		95% CI	(Reference)	(0.32-2.04)	(0.02-1.42)	(0.23-2.46)	(0.42-5.83)			
	Male	MV RR	1.00	0.82	0.48	0.70	0.73			0.70
		95% CI	(Reference)	(0.23-2.94)	(0.12-1.94)	(0.21-2.31)	(0.25-2.13)			
NLCS	Female	MV RR	1.00	1.03	1.44	1.27	1.93			0.13
		95% CI	(Reference)	(0.64-1.67)	(0.82-2.53)	(0.62-2.59)	(0.75-4.93)			
	Male	MV RR	1.00	1.27	0.80	0.68	1.42			0.50
		95% CI	(Reference)	(0.70-2.31)	(0.43-1.47)	(0.36-1.27)	(0.78-2.61)			
NYSC[§]	Female	MV RR	1.00	1.54	0.63	0.28	−			0.05
		95% CI	(Reference)	(0.75-3.15)	(0.17-2.33)	(0.03-2.27)	()			
	Male	MV RR	1.00	0.53	0.66	0.96	1.03			0.08
		95% CI	(Reference)	(0.29-1.00)	(0.33-1.34)	(0.46-1.98)	(0.48-2.22)			
NHS	Female	MV RR	1.00	1.02	0.91	0.77	1.58			0.28
		95% CI	(Reference)	(0.71-1.46)	(0.59-1.41)	(0.38-1.55)	(0.90-2.75)			
PLCO	Female	MV RR	1.00	1.00	0.59	0.57	2.16			0.21
		95% CI	(Reference)	(0.52-1.93)	(0.19-1.83)	(0.16-2.05)	(0.82-5.68)			
	Male	MV RR	1.00	1.31	1.05	1.13	1.38			0.64
		95% CI	(Reference)	(0.68-2.50)	(0.48-2.33)	(0.50-2.56)	(0.65-2.93)			
SMC[§]	Female	MV RR	1.00	0.72	0.53	1.73	−			0.68
		95% CI	(Reference)	(0.37-1.40)	(0.21-1.33)	(0.53-5.60)	()			
Females										
Cases			445	370	171	91	71			
Pooled		Age RR	1.00	1.04	0.89	1.15	1.63	0.89		0.001
		95% CI	(Reference)	(0.90-1.20)	(0.74-1.07)	(0.90-1.47)	(1.26-2.11)			
		MV RR	1.00	1.04	0.87	1.09	1.41	0.92		0.04
		95% CI	(Reference)	(0.90-1.20)	(0.72-1.06)	(0.86-1.39)	(1.07-1.85)			
Males										
Cases			207	268	245	147	172			
Pooled		Age RR	1.00	0.99	0.95	0.88	1.21	0.52		0.11
		95% CI	(Reference)	(0.81-1.19)	(0.78-1.15)	(0.71-1.10)	(0.98-1.49)			
		MV RR	1.00	0.98	0.94	0.86	1.12	0.51		0.33
		95% CI	(Reference)	(0.81-1.19)	(0.78-1.15)	(0.69-1.08)	(0.89-1.39)			
Overall										
Cases			652	638	416	238	243			
Pooled		Age RR	1.00	1.02	0.92	1.00	1.36	0.68	0.08	0.001
		95% CI	(Reference)	(0.91-1.14)	(0.80-1.05)	(0.85-1.18)	(1.15-1.60)			
		MV RR	1.00	1.02	0.91	0.96	1.22	0.80	0.19	0.05
		95% CI	(Reference)	(0.91-1.14)	(0.79-1.04)	(0.82-1.14)	(1.03-1.45)			

NOTE: Multivariate RRs (MV RR) were adjusted for smoking status (never smokers; past smokers, pack-years of <15 y; past smokers, pack-years of ≥15 y; current smokers, pack-years of <40 y, current smokers, pack-years of ≥40 y), history of diabetes (no, yes), BMI (continuously), and energy intake (continuously); age in years and year of questionnaire return were included as stratification variables.
*P value, test for between-studies heterogeneity is based on the ≥30 grams/d of alcohol category.
[†]P value, test for between-studies heterogeneity due to sex is based on the ≥30 grams/d of alcohol category.
[‡]P value, test for trend.
[§]New York State Cohort (females) and Swedish Mammography Cohort were excluded from the ≥30 grams/d category because there were no cases in that category. The participants who would have been in this category were included in the 15-29.9 grams/d category.

Table 3. Pooled age and multivariate adjusted RRs and 95% CIs for pancreatic cancer according to intake of alcohol from specific beverages

			Categories of alcohol intake (grams/d)			P-value, test for between-studies heterogeneity*	P-value, test for between-studies heterogeneity due to sex†	P-value, test for trend‡
Wine	All	Range	0	0.1-4.9	≥5			
		Cases	1071	694	284			
		Age RR (95% CI)	1.00 (Reference)	0.98 (0.89-1.08)	0.96 (0.83-1.10)	0.56	0.97	0.69
		MV RR (95% CI)	1.00 (Reference)	1.02 (0.93-1.13)	1.01 (0.87-1.16)	0.56	0.71	0.94
		MV RR (95% CI)§	1.00 (Reference)	1.00 (0.90-1.11)	0.99 (0.84-1.16)	0.36	0.88	>0.99
	Females	Cases	557	400	143			
		Age RR (95% CI)	1.00 (Reference)	1.00 (0.87-1.14)	0.95 (0.75-1.21)	0.20		0.76
		MV RR (95% CI)	1.00 (Reference)	1.03 (0.90-1.18)	0.97 (0.76-1.23)	0.24		0.84
		MV RR (95% CI)§	1.00 (Reference)	1.00 (0.86-1.15)	0.96 (0.71-1.28)	0.08		0.72
	Males	Cases	514	294	141			
		Age RR (95% CI)	1.00 (Reference)	0.96 (0.83-1.12)	0.96 (0.79-1.16)	0.89		0.61
		MV RR (95% CI)	1.00 (Reference)	1.02 (0.88-1.19)	1.03 (0.85-1.26)	0.84		0.94
		MV RR (95% CI)§	1.00 (Reference)	1.00 (0.85-1.18)	1.00 (0.81-1.24)	0.91		0.93
Beer	All	Cases	1228	518	303			
		Age RR (95% CI)	1.00 (Reference)	1.04 (0.89-1.20)	1.18 (0.94-1.48)	0.03	0.37	0.20
		MV RR (95% CI)	1.00 (Reference)	1.04 (0.89-1.21)	1.13 (0.90-1.04)	0.06	0.64	0.40
		MV RR (95% CI)§	1.00 (Reference)	1.04 (0.89-1.24)	1.09 (0.87-1.38)	0.05	0.76	0.37
	Females	Cases	861	191	48			
		Age RR (95% CI)	1.00 (Reference)	1.03 (0.81-1.30)	1.35 (0.91-1.99)	0.23		0.17
		MV RR (95% CI)	1.00 (Reference)	1.01 (0.79-1.29)	1.21 (0.87-1.68)	0.44		0.23
		MV RR (95% CI)§	1.00 (Reference)	1.00 (0.76-1.30)	1.06 (0.76-1.49)	0.34		0.44
	Males	Cases	367	327	255			
		Age RR (95% CI)	1.00 (Reference)	1.02 (0.85-1.23)	1.11 (0.83-1.46)	0.03		0.52
		MV RR (95% CI)	1.00 (Reference)	1.03 (0.86-1.22)	1.10 (0.82-1.48)	0.02		0.63
		MV RR (95% CI)§	1.00 (Reference)	1.06 (0.84-1.34)	1.14 (0.83-1.59)	0.01		0.54
Spirits‖	All	Cases	1092	523	434			
		Age RR (95% CI)	1.00 (Reference)	1.07 (0.96-1.20)	1.14 (1.00-1.29)	0.62	0.31	0.09
		MV RR (95% CI)	1.00 (Reference)	1.05 (0.93-1.17)	1.05 (0.93-1.19)	0.60	0.55	0.67
		MV RR (95% CI)§	1.00 (Reference)	1.03 (0.90-1.18)	1.04 (0.91-1.19)	0.73	0.42	0.74
	Females	Cases	718	242	140			
		Age RR (95% CI)	1.00 (Reference)	1.09 (0.93-1.27)	1.22 (1.01-1.47)	0.69		0.02
		MV RR (95% CI)	1.00 (Reference)	1.05 (0.90-1.23)	1.11 (0.91-1.34)	0.72		0.73
		MV RR (95% CI)§	1.00 (Reference)	1.06 (0.90-1.26)	1.11 (0.91-1.36)	0.85		0.26
	Males	Cases	374	281	294			
		Age RR (95% CI)	1.00 (Reference)	1.04 (0.85-1.28)	1.07 (0.91-1.27)	0.41		0.68
		MV RR (95% CI)	1.00 (Reference)	1.02 (0.82-1.28)	1.02 (0.84-1.23)	0.31		0.75
		MV RR (95% CI)§	1.00 (Reference)	0.97 (0.73-1.28)	1.00 (0.82-1.20)	0.39		0.68

NOTE: Age adjusted RRs were adjusted for age and calendar year. Multivariate RRs (MV RR) were adjusted for smoking status (never smokers; past smokers, pack-years of <15 y; past smokers, pack-years of ≥15 y; current smokers, pack-years of <40 y, current smokers, pack-years of ≥40 y), history of diabetes (no, yes), BMI (continuously), and energy intake (continuously); age in years and year of questionnaire return were included as stratification variables. New York State Cohort was not included in these analyses because they did not measure consumption of alcohol from specific beverages.

*P value, test for between-studies heterogeneity is based on the ≥5 grams/d of alcohol category.

†P value, test for between-studies heterogeneity due to sex is based on the ≥5 grams/d of alcohol category.

‡P value, test for trend.

§Multivariate RRs were additionally adjusted for consumption of the other 2 beverages (eg., alcohol intake from beer is also adjusted for alcohol intake from wine and spirits).

‖Swedish Mammography Cohort and the Melbourne Collaborative Cohort Study (Females) were not included in the ≥5 grams/d category because there were no cases in that category. The participants who would have been in this category were included in the 0.1-4.9 grams/d category.

(93, 94). Subtype analyses were conducted among this histology because it is the most common. SAS software (95), version 9.1, was used for all analyses.

Results

The total study sample consisted of 319,716 men and 542,948 women among whom 2,187 developed pancreatic cancer over 6.7 million person-years (Table 1). The percentage of alcohol drinkers at baseline in each study ranged from 45% to 92%. Median total alcohol intake among drinkers ranged from 1.6 grams/day in the female cohort of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial to 17.3 grams/day in the male cohort of the Melbourne Collaborative Cohort Study.

Slight positive associations with pancreatic cancer risk were only observed for the highest category of intake of total alcohol overall (pooled age-adjusted RR, 1.36; 95% CI, 1.15-1.60; and multivariate RR, 1.22; 95% CI, 1.03-1.45 comparing ≥30 to 0 grams/day of alcohol) and in females (pooled age-adjusted RR, 1.63; 95% CI, 1.26-2.11; and multivariate RR, 1.41; 95% CI, 1.07-1.85 comparing ≥30 to 0 grams/day of alcohol; Table 2). No statistically significant association was observed in men (pooled age-adjusted RR, 1.21; 95% CI, 0.98-1.49; and multivariate RR, 1.12; 95% CI, 0.89-1.39 comparing ≥30 to 0 grams/day of alcohol); however, the results between women and men were not significantly different (P-value, test for between-studies heterogeneity due to sex = 0.19). Overall, none of the study-specific RRs was statistically significant; however, most of the study-specific RRs exceeded 1 when comparing total alcohol intake of ≥30 to 0 grams/day. There was no statistically significant between-studies heterogeneity for the ≥30 grams/day category of alcohol intake for men, women, and overall (P value, test for between-studies heterogeneity >0.50). The pooled RRs were similar to those obtained when the studies were combined into a single data set (data not shown). When examining the same contrast excluding personal history of diabetes as a covariate from the model, the risk estimates were similar to the overall results (pooled multivariate RR, 1.21; 95% CI, 1.02-1.43; P value, test for trend = 0.07; P value, test for between-studies heterogeneity = 0.81; P value, test for between-studies heterogeneity due to sex = 0.22). Risk estimates for total alcohol intake were slightly stronger for adenocarcinomas of the pancreas overall (N$_{cases}$, 1,491; pooled multivariate RR, 1.45; 95% CI, 1.17-1.79; P value, test for between-studies heterogeneity = 0.92; P value, test for between-studies heterogeneity due to sex = 0.36), among men (pooled multivariate RR, 1.33; 95% CI, 1.00-1.77; P value, test for between-studies heterogeneity = 0.62), and among women (pooled multivariate RR, 1.62; 95% CI, 1.18-2.23; P value, test for between-studies heterogeneity = 0.95) when comparing ≥30 to 0 grams/day of alcohol.

When we examined a larger contrast in intake of total alcohol in men, a stronger risk of pancreatic cancer was observed among men who consumed ≥60 grams/day of alcohol compared with 0 grams/day [pooled multivariate RR (95% CI), 1.02 (0.76-1.36) for 30-44.9 grams/day of alcohol, 1.14 (0.79-1.64) for 45-59.9 grams/day, and 1.53 (1.10-2.12) for ≥60 grams/day (number of cases = 51)

compared with nondrinkers; P value, test for between-studies heterogeneity = 0.98 for ≥60 grams/day category; P value, test for trend = 0.05]. We were unable to examine the same contrast in women due to the small number of women consuming ≥45 grams/day of alcohol. Risk estimates were slightly stronger when we limited the cases to adenocarcinomas of the pancreas [pooled multivariate RR (95% CI), 1.22 (0.85-1.76) for 30-44.9 grams/day of alcohol, 1.21 (0.77-1.90) for 45-59.9 grams/day, and 1.59 (1.03-2.45) for ≥60 grams/day compared with 0 grams/day, P value, test for between-studies heterogeneity = 0.85 for ≥60 grams/day category; P value, test for trend = 0.05]. Estimates for pancreatic cancer risk were similar when excluding nondrinkers (comparing ≥30 to 0.1-4.9 grams/day intake of alcohol; data not shown).

No association was observed for alcohol from wine (pooled multivariate RR, 1.01; 95% CI, 0.87-1.16), beer (pooled multivariate RR, 1.13; 95% CI, 0.90-1.04), or spirits (pooled multivariate RR, 1.05; 95% CI, 0.93-1.19) and pancreatic cancer risk comparing ≥5 to 0 grams/day (Table 3). Results were similar when we mutually adjusted for alcohol from other specific beverages (e.g., when examining intake of alcohol from wine, we adjusted for intake of alcohol from beer and alcohol from spirits). Overall, risk estimates for alcohol from wine, beer, and spirits were similar for adenocarcinoma of the pancreas. When we examined a larger contrast in intake of alcohol from beer and spirits in men, namely ≥15 grams/day compared with 0 grams/day, no statistically significant associations were observed between alcohol from beer (pooled multivariate RR, 1.15; 95% CI, 0.86-1.53) or alcohol from spirits (pooled multivariate RR, 1.14; 95% CI, 0.88-1.47) and pancreatic cancer risk. Due to the small number of men consuming >15 grams/day of alcohol from wine and women consuming higher amounts of alcohol from wine, beer, and spirits (≥15 grams/day), we were unable to evaluate the same contrast for these beverages.

Because smoking was the most influential confounder in our analyses, we conducted additional analyses to evaluate the effect of controlling for smoking habits using different parameterizations. The results were similar among the different models (data not shown). For example, when we controlled for smoking habits using smoking status (never, former, and current) as the covariate, the pooled multivariate RR comparing ≥30 to 0 grams/day of alcohol intake was 1.25 (95% CI, 1.05-1.48; P value, test for between-studies heterogeneity = 0.77). Similarly, when using smoking status, smoking duration among past smokers, and smoking dose among current smokers as the covariate, the pooled multivariate RR was 1.22 (95% CI, 1.03-1.45; P value, test for between-studies heterogeneity = 0.77) for the same contrast.

The nonparametric regression analyses showed a linear association between alcohol intake and pancreatic cancer risk overall (P value, test for linearity >0.10; pooled multivariate RR, 1.06; 95% CI, 1.02-1.10 for an increment of 15 grams/day of alcohol; P value, test for between-studies heterogeneity = 0.88; P value, test for between-studies heterogeneity due to sex = 0.77). The association between alcohol intake and pancreatic cancer risk was similar when we excluded personal history of diabetes as a covariate from the model (pooled multivariate RR, 1.05; 95% CI, 1.01-1.09 for a 15 grams/day

Table 4. Pooled multivariate RRs and 95% CIs for a 15 gram/d increment in total alcohol intake by levels of other pancreatic cancer risk factors (Continuous Model)

Factor	Cases	RR (95% CI)	P-value, test for between-studies heterogeneity	P-value, test for between-studies heterogeneity due to sex	P-value, test for interaction
Lifestyle factors					
Smoking status					
Never[*],[†]	762	0.96 (0.85-1.08)	0.95	0.14	0.91
Past[*],[‡]	658	1.07 (0.99-1.15)	0.33	0.87	
Current[§]	643	1.07 (0.99-1.16)	0.06	0.62	
BMI (kg/m^2)					
<25	929	1.12 (1.06-1.17)	0.96	0.45	0.01
≥25	1189	1.01 (0.95-1.07)	0.76	0.21	
Nutritional					
Methionine Intake[∥],[¶]					
Low	978	1.07 (1.02-1.12)	0.77	0.53	0.45
High	901	1.02 (0.93-1.12)	0.33	0.93	
Total folate intake[¶],[**]					
Low	1033	1.10 (1.04-1.16)	0.54	0.39	0.32
High	986	1.02 (0.95-1.09)	0.66	0.65	
Multivitamin use[††]					
No	1413	1.08 (1.02-1.13)	0.32	0.06	0.91
Yes	588	1.08 (1.01-1.16)	0.70	0.28	

NOTE: Multivariate RRs were adjusted for smoking status (never smokers; past smokers, pack-years of <15 y; past smokers, pack-years of ≥15 y; current smokers, pack-years of <40 y, current smokers, pack-years of ≥40 y), history of diabetes (no, yes), BMI (continuously), and energy intake (continuously); age in years and year of questionnaire return were included as stratification variables. In the smoking stratified analyses, past and current smoking analyses included pack-years (<15 years, ≥15 y for past smokers; <40 y, ≥40 y for current smokers) in the model; age in years and year of questionnaire return were included as stratification variables. For each model, the stratification variable was excluded as a covariate.

[*] Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial was excluded from the never and past smoking analyses because this study only included current smokers.

[†] Netherlands Cohort Study (Males) was excluded from the never smoking analysis due to small case numbers ($n < 10$).

[‡] Melbourne Collaborative Cohort Study (Females) and New York State Cohort (Males) were excluded from the past smoking analysis due to small case numbers ($n < 10$).

[§] Melbourne Collaborative Cohort Study (Males and Females) were excluded from the current smoking analysis due to small case numbers ($n < 10$).

[∥] California Teachers Study, Cohort of Swedish Men, Melbourne Collaborative Cohort Study (Males and Females) and Swedish Mammography Cohort were excluded from these analyses because they did not measure methionine intake.

[¶] The high versus low intakes were based on the median cutpoint of that nutrient within each study included in the pooled analysis. For total folate intake, we included both dietary and supplemental sources of folate.

[**] Canadian National Breast Screening Study, and Melbourne Collaborative Cohort Study were excluded from these analyses because they did not measure folate intake from supplemental sources.

[††] Canadian National Breast Screening Study was excluded from this analysis because data on multivitamin use was not available.

increment of total alcohol; P value, test for between-studies heterogeneity = 0.92; P value, test for between-studies heterogeneity due to sex = 0.79) or when the study sample was limited to nondiabetics (pooled multivariate RR, 1.05; 95% CI, 1.01-1.10 for a 15 grams/day increment of total alcohol; P value, test for between-studies heterogeneity = 0.92; P value, test for between-studies heterogeneity due to sex = 0.31).

Among the 10 studies that assessed alcohol intake in their validation studies (74-82),[24] the pooled age- and energy-adjusted RR for an increment of 15 grams/day of alcohol (equivalent to approximately one serving of alcohol) changed from 1.08 (95% CI, 1.04-1.13) to 1.10 (95% CI, 1.04-1.18; P value, test for between-studies heterogeneity = 0.44; P value, test for between-studies heterogeneity due to sex = 0.07) after correction for measurement error in the assessment of alcohol consumption.

The association between total alcohol intake and pancreatic cancer risk was not modified by smoking status, total folate intake, methionine intake, and multivitamin use (Table 4). However, a positive association

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[24] Wolk et al., personal communication.

(pooled multivariate RR, 1.12; 95% CI, 1.06-1.17 for a 15 grams/day increment of total alcohol intake) was restricted to normal weight individuals (BMI, ≤25 kg/m^2); no association (pooled multivariate RR, 1.01; 95% CI, 0.95-1.07) was observed among overweight and obese individuals (BMI, ≥25 kg/m^2; P value, test for interaction = 0.01). Although there was no statistically significant heterogeneity due to sex for the alcohol-pancreatic cancer association within each of the BMI strata ($P > 0.21$), the association for a 15 grams/day increment of total alcohol was modified by BMI only among men (pooled multivariate RR, 1.09; 95% CI, 1.02-1.18 among normal weight individuals; pooled multivariate RR, 0.99; 95% CI, 0.93-1.07 among overweight and obese individuals; P value for interaction = 0.05); no modification was present in women (pooled multivariate RR, 1.08; 95% CI, 0.98-1.19 among normal weight individuals; pooled multivariate RR, 1.07; 95% CI, 0.95-1.22 among overweight and obese individuals; P value for interaction = 0.95). A stronger positive association between alcohol intake and pancreatic cancer risk was observed among individuals with low total (dietary and supplemental) folate intake (pooled multivariate RR, 1.09; 95% CI, 1.04-1.14 for a 15 grams/day increment of total alcohol), whereas the association

was null for individuals with high total folate intake (pooled multivariate RR, 1.04; 95% CI, 0.98-1.11 for a 15 grams/day increment of total alcohol intake; P value, test for interaction = 0.32). A similar trend was observed when examining low and high intake of methionine.

In addition, the RRs for total alcohol did not differ when the cases were stratified into 2 groups defined by median age at diagnosis (ages <69 and ≥69 years; data not shown). When we excluded pancreatic cancer cases that arose during the first 2 years of follow-up, risk estimates were similar to the main results overall, in males, and in females (data not shown). Sensitivity analyses were conducted in which we compared results from analyses limited to the first 5 years of follow-up to those from analyses after 5 or more years of follow-up. Alcohol intake was positively associated with risk of pancreatic cancer in the first 5 years of follow-up (RR, 1.12; 95% CI, 1.06-1.18 for a 15 grams/day increment of total alcohol; P value, test for between-studies heterogeneity = 0.80) but not for after 5 years of follow-up years (RR, 1.01; 95% CI = 0.96-1.07 for a 15 grams/day increment of total alcohol; P value, test for between-studies heterogeneity = 0.85; P value, test for interaction = 0.004).

Discussion

In this pooled analysis that prospectively assessed the association between alcohol consumption and pancreatic cancer risk, weak positive associations were observed for alcohol intake of ≥30 grams/day compared with non-drinkers overall and among women. Although no statistically significant association was observed in men for the same comparison, there was no statistically significant modification of the association by sex. No statistically significant between-studies heterogeneity was present for these analyses indicating that the differences in the risk estimates among the cohorts were compatible with random variation. Weak positive but nonstatistically significant, associations were observed in the majority of studies included in this pooled analysis. The nonsignificant association observed between alcohol intake and pancreatic cancer risk in each study may be the result of the small case numbers of pancreatic cancer (≤150 pancreatic cancer cases in 9 of the cohort studies included in this pooled analysis) and the relatively small number of heavier drinkers within each study (range of the number of pancreatic cancer cases in the ≥30 grams/day category, 4-36).

Most (15-29, 31-34, 45, 50, 51, 55), but not all (35-44, 56), case-control studies and cohort studies have observed no association between alcohol intake and pancreatic cancer risk. However, most studies were unable to examine the association between higher intakes of alcohol (>45 grams/day) and pancreatic cancer risk. Due to small proportion of women in the studies we analyzed who reported drinking >45 grams of alcohol per day, we were unable to evaluate associations with heavier drinking in women. In men, positive associations between higher alcohol intake (>60 compared with 0 grams/day) and risk of pancreatic cancer were observed. Several case-control studies (15, 21, 29, 30, 39, 41-43) have examined the association between consumption of >3 alcoholic drinks per day (>45 grams of alcohol per day) and pancreatic cancer risk with approximately

half of the studies reporting a positive association (29, 39, 41, 42). Few of the prospective studies that were not included in our analysis because they did not meet our inclusion criteria have examined the risk of pancreatic cancer with relatively high intakes of alcohol. In the Japanese Collaborative Cohort study, no association was observed with pancreatic cancer risk among individuals who consumed >60 grams/day of alcohol compared with nondrinkers (96). However, in a record linkage study in Sweden, alcoholics (as defined on inpatient registries) compared with the general population had an ~40% increased risk of pancreatic cancer (55). As we observed in our analysis, no published case-control and cohort studies have observed a statistically significant interaction by sex for the association between alcohol intake and pancreatic cancer risk.

In addition, a statistically significant interaction by BMI was observed for the association between alcohol intake and pancreatic cancer risk. In men, the effect was stronger among those with a BMI of <25 kg/m^2 (classified as normal weight) than among those with a BMI of ≥25 kg/m^2. Overweight and obesity are hypothesized to be associated with a higher risk of pancreatic cancer (57), and the association between alcohol intake and pancreatic cancer risk is not evident in this high-risk group.

Besides the cohort studies in our pooled analysis (54, 71, 97), we are unaware of other case-control and prospective cohort studies that have examined the joint effects of alcohol and folate intake on pancreatic cancer risk. Although our results for alcohol intake did not vary significantly by total folate intake (P value, test for interaction = 0.45), a positive association between alcohol intake and pancreatic cancer risk was observed only among individuals with low total folate intake; the association was attenuated among individuals with high total folate intake. Alcohol has been shown to affect folate bioavailability and interrupt critical folate-driven biological processes; inadequate levels of folate can disrupt DNA methylation, synthesis, and repair (98). Therefore, it is plausible that alcohol consumption may only affect pancreatic cancer risk among individuals with low folate intake (98). A similar interaction between folate and alcohol intake has been observed for risk of colorectal (99) and breast cancer (100-104).

Because our analyses were conducted using only a baseline FFQ covering recent intake, we were not able to assess changes in intakes over time, nor were we able to evaluate lifetime consumption of alcohol, past drinking habits, and binge drinking patterns. Although we are not able to measure lifetime alcohol drinking patterns, a national survey found moderate to good correlations ($r = 0.63$; ref. 105) for alcohol intake from estimates that were collected 10 years apart; thus, baseline measurement of alcohol intake may represent more longer term intakes reasonably well. Only a few studies have addressed these additional ways (e.g., changes in consumption; lifetime drinking patterns) to examine alcohol drinking habits in relation to pancreatic cancer risk; the results have been inconclusive (20, 26). Additionally, because most of the studies only measured alcohol intake in adulthood, we may not have captured the relevant exposure time for pancreatic carcinogenesis if exposures in younger adult life are important.

Furthermore, we could not examine chronic long term exposure to high intakes of alcohol, which may be even more important in the development of pancreatic cancer. Animal studies have examined the pathophysiologic changes and injuries to the pancreas by acute and chronic alcohol exposure. Acute alcohol exposure alone has not produced damage or injury to the pancreas; however, chronic alcohol exposure has lead to pancreatic damage and morphologic changes such as necrosis, elevation of oxidative stress markers, and chronic inflammatory cell infiltration in some, but not all, studies (106).

We were unable to examine associations of alcohol intake by tumor site or microscopic confirmation status because few studies had these data available. Thus, our pancreatic cancer case definition may represent different subtypes of pancreatic cancer, and individual subtypes may be associated with different etiologies. However, the majority of pancreatic cancer cases occur in the exocrine portion of the pancreas (~95%), develop within the head or neck region, and are classified histologically as adenocarcinomas (~90%; refs. 58-62). In our analyses, when the case definition for pancreatic cancer was limited to adenocarcinomas, we observed slightly higher risk estimates for higher intakes of alcohol.

In the studies comprising this pooled analysis, diet was measured before diagnosis of pancreatic cancer; thus, a cancer diagnosis would not have influenced the reporting of alcohol intake. A strength of our study was our ability to correct for measurement error in alcohol intake in most of the included studies. The measurement-error corrected risk estimates were similar to the uncorrected results, which was expected because the assessments of alcohol intake from the study-specific questionnaires and multiple 24-hours recalls or food records generally have been shown to be highly correlated (74-82).[25]

Although our categorization of covariates was predetermined according to how each study assessed the covariates on their questionnaires, one advantage of our study was that we were able to standardize the covariates to include in the model and to model these covariates uniformly. We also classified the main exposures similarly across studies, thereby lessening potential sources of heterogeneity across studies. Within our models, we adjusted for most of the important known pancreatic cancer risk factors. The majority of studies collected information on age, smoking status, diabetes, and height and weight, thus capturing information on the few consistently reported risk factors for pancreatic cancer. In studies that measured all of the covariates that were included in our multivariate models, results from the age-adjusted and multivariate models were similar, suggesting that confounding was minimal. Because smoking was the most influential confounder in our analyses related both to exposure (alcohol intake) and disease (pancreatic cancer), we cannot completely rule out residual confounding by smoking in our results. Measurement error in smoking habits (e.g., duration and number of cigarettes smoked) and status (e.g., never, former, current smoker) and variations in other unmea-

sured aspects may have an effect on the estimation of the risk of pancreatic cancer from other factors correlated with smoking, such as alcohol. However, we observed no difference between the risk estimates for the association between alcohol intake and pancreatic cancer risk when applying different parameterizations of the smoking variables in our statistical models. Due to the inclusion of 14 cohort studies, we had far greater statistical power than any individual cohort study to examine whether associations differed for population subgroups.

In summary, a weak positive association between alcohol intake during adulthood and pancreatic cancer risk was observed in the highest category of intake (≥30 grams/day or ~2 alcoholic beverages per day). Associations with alcohol intake were stronger among individuals who were normal weight. Thus, our findings are consistent with a modest increase in risk of pancreatic cancer for alcohol intakes of at least 30 grams/day.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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