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Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan)

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Abstract The literature has consistently reported no association between low to moderate alcohol consumption and pancreatic cancer; however, a few studies have shown that high levels of intake may increase risk. Most single studies have limited power to detect associations even in the highest alcohol intake categories or to examine

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associations by alcohol type. We analyzed these associations using 1,530 pancreatic cancer cases and 1,530 controls from the Pancreatic Cancer Cohort Consortium (PanScan) nested case–control study. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression, adjusting for potential confounders. We observed no significant overall association between total alcohol (ethanol) intake and pancreatic cancer risk (OR = 1.38, 95% CI = 0.86–2.23, for 60 or more g/day vs. >0 to <5 g/day). A statistically significant increase in risk was observed among men consuming 45 or more grams of alcohol from liquor per day (OR = 2.23, 95% CI = 1.02–4.87, compared to 0 g/day of alcohol from liquor,   P-trend = 0.12),   but   not   among   women (OR = 1.35, 95% CI = 0.63–2.87, for 30 or more g/day of alcohol from liquor, compared to none). No associations were noted for wine or beer intake. Overall, no significant increase in risk was observed, but a small effect among heavy drinkers cannot be ruled out.

Keywords   Alcohol · Pancreatic cancer · Pooled analysis

Introduction

Worldwide, pancreatic cancer is the eighth leading cause of cancer death, and ∼227,000 men and women died of this cancer in 2002 [1]. By decreasing exposure to risk factors of pancreatic cancer, it may be possible to reduce pancreatic cancer mortality, which thus far has been difficult to achieve given the lack of effective treatments, high fatality rates, and difficulty in detecting cancer at early stages. Currently established risk factors for pancreatic cancer include cigarette smoking, which is estimated to account for 20% of pancreatic cancers [2], type II diabetes [3], obesity [4], and chronic pancreatitis [5, 6].

As alcohol abuse is a cause of chronic pancreatitis, it has been postulated that excessive alcoholic intake could increase the risk of pancreatic cancer indirectly through this pathway. A large number of studies, including most cohort studies, have reported no association between alcohol intake and pancreatic cancer risk [7–15], while seven studies reported an elevated pancreatic cancer risk with high alcohol intake [16–22]. Increased risk of pancreatic cancer has also been observed among alcoholics [23–26]. Most cohort studies have limited power to detect associations in the highest categories of alcohol intake and to examine higher intakes of different alcoholic beverages. A recent pooled cohort analysis reported a statistically significant 22% increase in risk among those consuming 30 or more grams of alcohol per day compared to none [27]. To address these issues, we examined the association between alcohol intake and pancreatic cancer risk using the pooled nested case–control samples from 12 prospective cohort studies in the Pancreatic Cancer Cohort Consortium (PanScan).

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Materials and methods

Study population

The PanScan study, which includes pancreatic cancer cases and controls pooled from 12 prospective cohort studies and one case–control study, was formed primarily to identify genome-wide associations (GWA) and to investigate gene–environment interactions. The cohorts included in PanScan were those participating in the NCI Cohort Consortium that were willing to participate in this effort. The main results for the GWA are published [28, 29]. The current analysis is based on the pooled case–control data set from the 12 prospective cohort studies (we excluded the case–control study given the different study design). The following cohorts contributed data and were included in this analysis: the Alpha-Tocopherol, Beta-Carotene Prevention Study (ATBC) [30], Clue II [31], Cancer Prevention Study II (CPS II) [32], European Prospective Investigation into Cancer and Nutrition (EPIC) [33], The New York University Women's Health Study (NYU-WHS) [34], The Prostate, Lung, Colorectal, Ovarian Cancer Screening Trial (PLCO) [35], Shanghai Men's and Women's Health Study (SMWHS) [36, 37], the Women's Health Initiative (WHI) [38], the Nurses' Health Study (NHS) [39], the Health Professionals Follow-up Study (HPFS) [40], the Women's Health Study (WHS) [41], and the Physicians' Health Study (PHS) [42]. Details on the cases and controls included in PanScan from these cohorts are given in Table 1. A total of 1,530 cases and 1,530 controls were available for this analysis.

Case ascertainment and data collection

Cases included all incident primary pancreatic adeno-carcinoma (ICD-O-3 code C250-C259 or C25.0-C25.3, C25.7-C25.9). We excluded endocrine pancreatic tumors (C25.4, histology type, 8150, 8151, 8153, 8155, 8240, 8246). All cases were confirmed through cancer registries (ATBC, EPIC, HPFS, NHS, SMWHS, CPS II), death certificates (CPS II, EPIC, HPFS, NHS, NYU-WHS, PHS-1, WHS), and/or review of medical records by medical personnel (ATBC [through 1999], EPIC, HPFS, NHS, NYU-WHS, PHS-1, PLCO, SMWHS, WHS).

Controls were frequency matched to cases (1:1 ratio) on calendar year of birth (± 5 years), sex, race, and length of follow-up and were alive and cancer free on the incidence date of the matched case. Each cohort may have been matched additionally on other relevant factors such as age at baseline or age at blood draw (± 5 years), date/time of day of blood draw, fasting blood draw, and smoking status.

Data on alcohol consumption, age, sex, cigarette smoking history, race, BMI, history of diabetes, folate intake, and other dietary data were obtained from each study contributing to PanScan. In addition, data on family

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history of pancreatic cancer were available for seven of the studies.

The Special Studies Institutional Review Board (SSIRB) of the National Cancer Institute approved the pooled Pan-Scan study. Each study was approved by its local IRB.

Measurement of alcohol exposure

Baseline alcohol consumption was obtained by questionnaire in each of the studies. For studies which did not provide intake in grams of ethanol per day, it was calculated for each alcoholic beverage (i.e., 13.72 g ethanol for 5 oz of wine; 12.96 g ethanol for 12 oz of beer; and 13.93 g ethanol for 1.5 oz of liquor) by multiplying these values to the reported consumption of these beverages (which reflects consumption over the preceding year). Total alcohol intake was created by calculating grams of ethanol per day across all alcoholic beverages. For Clue II, 12 g of ethanol per drink was used regardless of type of drink, given a precedent already set within this cohort. For PHS, intake of grams of ethanol (13.54 g of ethanol per drink) was computed from frequency data for overall alcohol intake as data on different types of alcoholic beverages were not available. For SMWHS, alcohol intake was measured in the Chinese measure *liangs*; intake of grams of ethanol per day was estimated by assuming 50 g/liang and multiplying by % of ethanol in different alcoholic beverages and frequency consumed (rice wine was included in the total alcohol variable but not in the liquor or wine variables).

Statistical analysis

We calculated odds ratios (OR) and 95% confidence intervals (95% CI) for pancreatic cancer risk using unconditional logistic regression. All models were adjusted for established risk factors of pancreatic cancer: age (continuous), cohort, sex, cigarette smoking history (never, former quit >10 years, former quit <10 years, current <20 cigarettes/day, current 20 cigarettes/day, current >20 cigarettes/day, unknown), race (Caucasian, Asian, other), BMI (continuous, kg/m^2), and self-reported diabetes (yes, no, missing). For the total alcohol analysis, we used the lowest category of alcohol (>0 to <5 g/day) as the referent category as the nondrinker category is likely to include past drinkers who quit drinking and thereby could have an elevated risk. For the specific types of alcohol, we compared consumption of each type of alcohol to those who reported none for that specific alcohol type; nondrinkers were included in the model as a separate category. The PHS cohort and EPIC-Umea center were removed from the specific alcohol analyses as they did not have information on type of alcohol. In addition, in the analysis for the specific types of alcohol, we mutually adjusted for the other types of alcohol. We did not adjust for family history of pancreatic cancer as only seven cohorts had collected this information. We tested for trend among consumers of alcohol by entering the median value among controls for each category and modeling this as a continuous variable.

Heterogeneity in the risk estimates for our study was assessed using the Q statistic and the I^2 statistic. We considered statistically significant heterogeneity at the $P = 0.05$ level of association. I^2 was used because it describes the percentage of variability in point estimates that is due to heterogeneity rather than sampling error. A value of I^2 of 50% or more was considered to be notably heterogeneous. To investigate whether one single study unduly influenced the pooled estimates, sensitivity analyses also were conducted to compare pooled risk estimates after systematically excluding each study in turn. Finally, we conducted stratified analyses by sex, smoking status, and BMI, as they are established risk factors of pancreatic cancer, as well as folate intake, since alcohol can influence folate metabolism and DNA methylation. Tests for interactions were conducted by including the cross-product terms for alcohol (continuous) and the stratified variables in the logistic regression models (using BMI ≤ 25 and >25; never, former, and current smoker; low and high folate based on median cutpoint).

Results

Total alcohol (ethanol) consumption and individual alcoholic beverage intake varied by cohort study (Table 1). The Shanghai cohort (SMWHS) had the lowest alcohol consumption with only 10% of the total population consuming any alcohol (most of the participants are women). In contrast, 92% of the Physicians' Health Study (PHS) participants were current consumers of alcohol. In this pooled analysis, cases were more likely to have been smokers than controls (28.6 vs. 23.0%), to have a history of diabetes (10.4 vs. 6.8%), and to have a family history of pancreatic

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Table 1 Cohort characteristics and median daily intakes of alcohol among controls for study on alcohol and pancreatic cancer: PanScan

Cohort	Years of collection of alcohol data	Cases, n	Controls, n	Years of follow-up (median)	Baseline age range (years)	Baseline current drinkers, %	Median intake (10th and 90th percentiles) of alcohol (g/day) among controls who were drinkers			
							Total alcohol intake	Alcohol from wine	Alcohol from beer	Alcohol from liquor
ATBC	1985–1988	209	197	12	57–85	87.2	10.7 (1.7–41.2)	0 (0–2.2)	2.4 (0–14.2)	5.4 (0–23.8)
Clue II	1989	69	67	8	42–93	39.7	3.7 (0.8–49.5)	0 (0–9.4)	0.8 (0–30)	0 (0–9.4)
CPS II	1992–1993	154	155	10	64–90	59.9	6.6 (0.9–26.8)	1.0 (0–14.1)	0.9 (0–5.9)	0.9 (0–16.9)
EPIC	1992–2000	374	391	7	37–84	88.0	8.6 (0.8–47.2)	5.0 (0.2–31.6)	0.6 (0–18.0)	0.2 (0–4.2)
HPFS	1986	55	55	13	55–87	83.6	11.4 (1.0–38.4)	0.8 (0–8.8)	0.8 (0–10.2)	2.0 (0–35.0)
NHS	1980	88	88	23	47–80	73.9	6.6 (0.8–32.0)	0.8 (0–11.0)	0 (0–10.2)	1.0 (0–14.0)
NYU-WHS	1994–1997	10	12	12.5	48–81	40.9	9 (2.0–26.0)	5.0 (0–10.0)	0 (0–6.0)	0 (0–20.0)
PHS I	1982–1983	61	62	21	49–88	91.9	5.8 (5.8–40.6)	–	–	–
PLCO	1993–2001	136	140	6	56–84	83.0	4.8 (0.4–44.8)	0.2 (0–7.4)	0.2 (0–16.8)	0.4 (0–16.8)
SMWHS	1996 (women) 2001 (men)	78	79	3	43–77	6.4	12.4 (1.7–110.0)[a]	1.7[a]	12.5 (4.6–52.0)[a]	10.3 (2.9–60.0)[a]
WHI	1993–1998	256	244	4	53–88	67.4	3.4 (0.6–22.0)	0.8 (0–13.8)	0 (0–0.8)	0 (0–8.2)
WHS	1992–1993	40	40	10	47–82	58.8	5.6 (2.0–11.8)	1.8 (0.8–5.6)	1.0 (0–1.8)	0 (0–6.4)
Pooled		1,530	1,530	8	37–93	73.0	7.0 (0.8–40.6)	0.9 (0–13.6)	0.8 (0–12.0)	0.8 (0–14.0)

[a] Based on 8 observations for total alcohol, 1 observation for alcohol from wine, 4 observations for alcohol from beer, and 3 observations for alcohol from liquor

cancer (5.9 vs. 3.4% among the seven cohorts that provided these data). Dietary intake of folate, total and saturated fat were similar across cases and controls. BMI was significantly greater in cases than controls (P value = 0.02; data not shown).

Among controls (Table 2), men tended to drink more alcohol than women, and percent of current smokers and cigarette smoking intensity increased with increasing alcohol intake. Self-reported diabetics were less likely to consume alcohol. Total and saturated fat, and BMI, among controls, did not differ appreciably by alcoholic intake, but folate intake was lower with higher alcohol intake.

Figure 1 provides the study specific and pooled results for total alcohol intake based on the multivariate models (NYU-WHS and SMWHS are excluded from this plot because of insufficient numbers). Overall, 7 of 10 studies reported positive associations for total alcohol intake, while three were below unity. Studies with smaller numbers of cases and controls tended to show stronger associations, but these were all highly unstable estimates (NHS, HPFS, and WHS). The pooled OR for total alcohol intake

comparing those drinking 30 or more grams of alcohol per day to those who drank some alcohol (>0 to <10 g/day) was not statistically significant (OR = 1.23, 95% CI = 0.97–1.57). There was no statistically significant heterogeneity between cohorts in this study population when evaluating total alcohol consumption in the pooled estimates (compared to referent, <10 g/day, P = 0.94 for nondrinkers; P = 0.89 for 10 < 30 g/day; P = 0.90 for >30 g/day).

Unadjusted and adjusted pooled odds ratios and confidence intervals are presented in Table 3. Overall, total alcohol was not associated with a significant increase in risk of pancreatic cancer; controlling for smoking in the adjusted model attenuated the association in the top category of total alcohol intake. Similar associations were observed for men and women for total alcohol intake. In a sensitivity analysis, we observed a substantially lower pooled estimate for the top category of alcohol intake after removing the ATBC study (OR = 1.12, 95% CI = 0.66–1.90, comparing 60 or more g/day vs. >0 to <5 g/day), and a substantially higher pooled estimate after removing the

Table 2 Selected characteristics of controls according to daily alcohol consumption: PanScan (n = 1,530)

Characteristics	Alcohol consumption (g/day)				
	Nondrinker	>0 to <5	5 to <15	15 to <30	≥30
Men, %	31.0	39.1	56.5	58.4	76.3
Age at reference diagnosis (years), mean ± SD	70.0 ± 7.7	70.1 ± 8.0	69.6 ± 7.5	69.2 ± 8.1	67.4 ± 7.6
Race					
Caucasian, %	72.8	95.9	97.1	98.9	97.7
African American, %	4.6	1.6	0	0	0
Asian, %	20.8	1.4	1.5	1.1	2.3
Other, %	0.8	0.9	0	0	0
Unknown, %	1.0	0.2	1.5	0	0
Smoking history					
Never smokers, %	61.2	45.0	34.2	27.5	14.5
Former smokers, %	25.4	35.7	39.4	36.0	49.1
Current smokers, %	13.2	19.1	25.8	35.4	35.8
Unknown, %	0.3	0.2	0.6	1.1	0.6
Smoking duration in smokers, mean ± SD	27.7 ± 14.7	26.8 ± 14.6	29.4 ± 15.5	30.2 ± 13.4	29.4 ± 13.6
No. of cigarettes per day in smokers, mean ± SD	18.4 ± 14.0	16.2 ± 12.9	18.6 ± 12.9	17.3 ± 9.7	21.0 ± 14.7
Body mass index (kg/m²), mean ± SD	26.3 ± 4.8	26.4 ± 4.2	26.0 ± 4.6	25.7 ± 3.7	26.2 ± 3.6
Family history of pancreatic cancer (1st degrees), %[a]	2.3	1.4	0.9	0.6	1.7
Self-reported diabetes, %	12.4	6.1	3.8	3.4	3.5
Dietary intake per day, mean ± SD					
Total fat (g/1,000 kcal)	34.5 ± 12.7	38.6 ± 8.7	39.5 ± 8.4	38.7 ± 8.4	35.7 ± 8.1
Saturated fat (g/1,000 kcal)	11.7 ± 5.4	14.3 ± 4.6	14.9 ± 4.7	14.7 ± 4.8	13.0 ± 4.1
Total folate intake (mg/1,000 kcal)	288 ± 218	264 ± 193	227 ± 172	212 ± 152	180 ± 120

SD standard deviation

[a] Information was available for ATBC, Clue II, CPS II, NHS, NYU-WHS, PLCO, and SMWHS
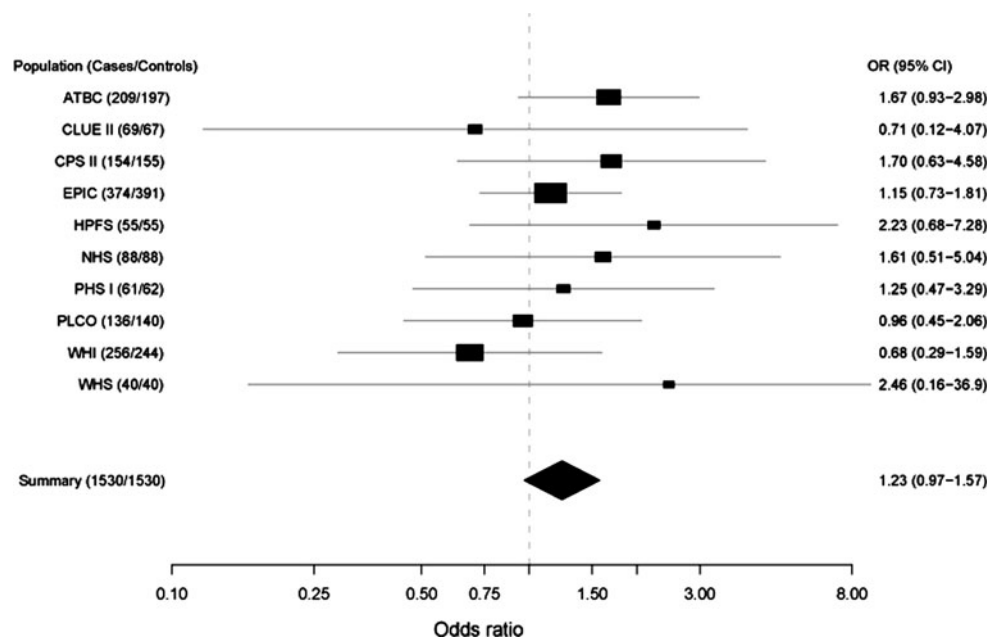
Fig. 1 Cohort-specific risk estimates for pancreatic cancer for daily consumption of ≥30 g alcohol compared to >0 to <10 g alcohol. Adjusted for age (continuous), sex (in sex combined models), race (Caucasian, Asian, other), smoking status (never, former smokers quit ≥10 years, former smokers quit <10 years, current smokers <20 cigarettes/day, current smokers = 20 cigarettes/day, current smokers >20 cigarettes/day, unknown), diabetes (yes, no, missing), and BMI (continuous). Solid squares represent the odds ratios. *Horizontal lines* represent 95% confidence intervals. *Solid diamond* presents the summary odds ratio and its 95% confidence interval. Test for heterogeneity ($P = 0.20$, $I^2 < 50\%$). NYU-WHS and SMWHS are excluded from this plot because of insufficient numbers

EPIC study (OR = 2.30, 95% CI = 1.13–4.68, comparing 60 or more g/day vs. >0 to <5 g/day). Exclusion of other studies did not influence the pooled estimates.

Among men, a statistically significant increase in risk was observed for the top category of alcohol intake from liquor (OR = 2.23, 95% CI = 1.02–4.87, 45 or more g/day vs. none, Table 3). Among women, liquor was not frequently consumed at the high levels (i.e., 45 or more g/day) so there was insufficient data to examine this association; no association was observed for the category of 30 or more grams of alcohol per day (vs. none). The association for alcohol from liquor was not statistically significant when men and women were combined (OR = 1.86, 95% CI = 0.95–3.64, 45 or more g/day vs. none). No associations were observed for grams of alcohol consumed from wine and beer (Table 3). *P* values for heterogeneity between cohort studies were not statistically significant for the different types of alcoholic beverages.

We examined alcohol intake by smoking status because smoking may modify the association between alcohol and pancreatic cancer (Table 4). Tests for interaction were not statistically significant, and there were no indications that the associations were modified by smoking status. A statistically significant association was observed for the second category of wine intake among current smokers;

however, given the lack of a dose–response trend across categories, this finding is most likely to be due to chance.

We observed no interactions for alcohol and BMI (*P* value = 0.87) or alcohol and folate intake (*P* value = 0.65). Furthermore, the overall pooled estimate for total alcohol intake was similar to the main findings (Table 3) after removing the first 2 and 5 years of follow-up (multivariable OR = 1.47, 95% CI = 0.90–2.41, and OR = 1.51, 95% CI = 0.88–2.60, respectively, for 60 or more g/day of alcohol vs. none).

Discussion

In this large pooled nested case–control study, we observed no significant overall increase in risk of pancreatic cancer with moderate to high levels of alcohol intake. The associations were similar when stratified by sex or smoking status. We observed a greater than twofold increase in risk among men drinking 45 or more grams of alcohol from liquor per day compared to none, but the same association was not statistically significant for men and women combined. Other alcoholic beverages were not associated with risk of pancreatic cancer and results from stratified analyses by smoking status, BMI, and folate intake and were similar to the overall findings.

Table 3 Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for alcohol consumption in relation to pancreatic cancer risk: PanScan

	Men			Women			Men and women combined		
	Cases/controls, n	OR (95% CI)[a]	OR (95% CI)[b]	Cases/controls, n	OR (95% CI)[a]	OR (95% CI)[b]	Cases/controls, n	OR (95% CI)[a]	OR (95% CI)[b]
	730/725			800/805			1,530/1,530		
Total alcohol (g/day)									
0	127/122	1.24 (0.87–1.76)	1.23 (0.86–1.75)	306/272	1.23 (0.95–1.59)	1.21 (0.93–1.59)	433/394	1.24 (1.01–1.53)	1.19 (0.97–1.48)
>0 to <5	146/172	1.00	1.00	254/268	1.00	1.00	400/440	1.00	1.00
5 to <10	134/123	1.31 (0.93–1.85)	1.31 (0.92–1.87)	68/105	0.68 (0.48–0.97)	0.71 (0.50–1.01)	202/228	0.96 (0.76–1.23)	1.00 (0.78–1.28)
10 to <15	59/72	0.96 (0.63–1.45)	0.94 (0.62–1.43)	59/45	1.40 (0.91–2.15)	1.49 (0.97–2.31)	118/117	1.11 (0.83–1.49)	1.15 (0.85–1.54)
15 to <30	112/104	1.25 (0.88–1.77)	1.29 (0.90–1.84)	61/74	0.85 (0.58–1.25)	0.87 (0.59–1.29)	173/178	1.05 (0.81–1.35)	1.08 (0.83–1.40)
30 to <45	81/62	1.57 (1.04–2.37)	1.66 (1.08–2.53)	38/31	1.24 (0.75–2.06)	1.17 (0.69–1.96)	119/93	1.37 (1.00–1.88)	1.36 (0.99–1.88)
45 to <60	31/39	0.91 (0.54–1.54)	0.91 (0.53–1.56)	14/10[c]	1.45 (0.63–3.33)	1.32 (0.56–3.09)	38/45	0.90 (0.57–1.42)	0.86 (0.54–1.37)
≥60	40/31	1.54 (0.91–2.60)	1.50 (0.88–2.57)	–	–	–	47/35	1.47 (0.92–2.34)	1.38 (0.86–2.23)
P-trend		0.11	0.11		0.30	0.41		0.06	0.11
OR_cont[d]		1.04 (0.98–1.11)	1.03 (0.97–1.11)		1.07 (0.93–1.24)	1.06 (0.91–1.23)		1.04 (0.98–1.11)	1.03 (0.97–1.10)
Alcohol from beer (g/day)									
0[e]	91/96	1.00	1.00	296/281	1.00	1.00	387/377	1.00	1.00
>0 to <5	224/231	1.01 (0.71–1.43)	0.98 (0.69–1.39)	137/180	0.69 (0.52–0.92)	0.70 (0.52–0.93)	361/411	0.83 (0.67–1.03)	0.82 (0.66–1.02)
5 to <10	85/78	1.10 (0.72–1.69)	1.13 (0.73–1.74)	20/25	0.73 (0.40–1.35)	0.78 (0.42–1.45)	105/103	0.94 (0.68–1.30)	0.97 (0.70–1.34)
10 to <15	36/42	0.89 (0.52–1.51)	0.86 (0.50–1.47)	22/14[c]	1.43 (0.71–2.87)	1.44 (0.70–2.99)	45/50	0.84 (0.54–1.31)	0.82 (0.52–1.28)
15 to <30	37/32	1.16 (0.66–2.05)	1.17 (0.65–2.08)	–	–	–	38/33	1.03 (0.62–1.72)	1.09 (0.65–1.83)
30 to <45	26/18	1.47 (0.75–2.89)	1.69 (0.83–3.42)	–	–	–	35/22	1.44 (0.82–2.53)	1.58 (0.88–2.84)
≥45	17/20	0.86 (0.42–1.76)	0.78 (0.37–1.64)	–	–	–	20/21	0.87 (0.46–1.66)	0.79 (0.41–1.54)
P-trend		0.59	0.60		0.36	0.48		0.29	0.38
OR_cont[d]		1.02 (0.93–1.13)	1.01 (0.91–1.12)		1.33 (0.93–1.91)	1.30 (0.89–1.88)		1.04 (0.95–1.14)	1.03 (0.93–1.13)
Alcohol from wine (g/day)									
0[e]	178/204	1.00	1.00	71/54	1.00	1.00	249/258	1.00	1.00
>0 to <5	206/188	1.47 (1.06–2.03)	1.49 (1.07–2.06)	255/285	0.69 (0.47–1.03)	0.79 (0.52–1.20)	461/473	1.09 (0.85–1.39)	1.17 (0.91–1.49)
5 to <10	57/44	1.74 (1.08–2.81)	1.76 (1.08–2.88)	70/76	0.70 (0.43–1.15)	0.84 (0.51–1.39)	127/120	1.17 (0.84–1.62)	1.28 (0.91–1.79)
10 to <15	25/31	1.13 (0.61–2.08)	1.20 (0.65–2.23)	39/50	0.59 (0.34–1.03)	0.74 (0.41–1.31)	64/81	0.87 (0.59–1.30)	1.02 (0.68–1.53)
15 to <30	20/17	1.50 (0.74–3.06)	1.57 (0.76–3.23)	24/21	0.86 (0.43–1.73)	0.99 (0.49–2.03)	44/38	1.25 (0.76–2.03)	1.39 (0.85–2.28)
30 to <45	16/16	1.48 (0.69–3.19)	1.61 (0.74–3.52)	16/15[c]	0.77 (0.34–1.72)	0.83 (0.36–1.89)	29/26	1.23 (0.68–2.20)	1.31 (0.73–2.37)
≥45	10/13	1.15 (0.47–2.81)	1.15 (0.46–2.86)	–	–	–	13/18	0.82 (0.38–1.75)	0.80 (0.37–1.72)
P-trend		0.98	0.83		0.86	0.97		0.76	0.85
OR_cont[d]		1.03 (0.87–1.22)	1.03 (0.87–1.23)		0.93 (0.73–1.18)	0.95 (0.74–1.21)		0.99 (0.86–1.14)	0.99 (0.86–1.14)

Table 3 continued

	Men			Women			Men and women combined		
	Cases/controls, n	OR (95% CI)[a]	OR (95% CI)[b]	Cases/controls, n	OR (95% CI)[a]	OR (95% CI)[b]	Cases/controls, n	OR (95% CI)[a]	OR (95% CI)[b]
Alcohol from liquor (g/day)									
0[e]	89/113	1.00	1.00	212/230	1.00	1.00	301/343	1.00	1.00
>0 to <5	224/223	1.29 (0.91–1.82)	1.31 (0.93–1.86)	183/192	1.02 (0.77–1.35)	0.99 (0.74–1.31)	407/415	1.11 (0.90–1.38)	1.10 (0.89–1.37)
5 to <10	75/67	1.45 (0.93–2.26)	1.43 (0.92–2.24)	27/33	0.87 (0.50–1.50)	0.80 (0.46–1.39)	102/100	1.16 (0.84–1.62)	1.13 (0.81–1.57)
10 to <15	28/39	0.88 (0.49–1.57)	0.87 (0.48–1.57)	24/19	1.44 (0.76–2.73)	1.44 (0.75–2.76)	52/58	1.02 (0.67–1.55)	1.00 (0.65–1.52)
15 to <30	61/42	1.80 (1.09–2.98)	1.67 (1.00–2.79)	10/13	0.83 (0.36–1.95)	0.74 (0.31–1.76)	71/55	1.46 (0.97–2.18)	1.33 (0.88–2.01)
30 to <45	15/18	1.05 (0.50–2.23)	1.03 (0.48–2.23)	19/13[c]	1.55 (0.74–3.25)	1.35 (0.63–2.87)	29/28	1.17 (0.67–2.03)	1.04 (0.59–1.81)
≥45	21/13	2.16 (1.01–4.61)	2.23 (1.02–4.87)	–	–	–	26/16	1.93 (1.00–3.71)	1.86 (0.95–3.64)
P-trend		0.06	0.12		0.22	0.46		0.03	0.11
OR$_{cont}$[d]		1.12 (0.98–1.28)	1.10 (0.95–1.27)		1.14 (0.90–1.43)	1.09 (0.86–1.37)		1.12 (1.00–1.26)	1.10 (0.97–1.23)

The P values for interaction of continuous alcohol (type) by sex are 0.67 (total alcohol), 0.20 (beer), 0.73 (wine), and 0.86 (liquor)

[a] Adjusted for age (continuous), cohort, and sex (in sex combined models). The specific types of alcohol were mutually adjusted for the other types of alcohol. The PHS cohort and EPIC-Umea center were removed from the specific alcohol beverage analyses as alcohol type was not available

[b] Adjusted for age (continuous), cohort, sex (in sex combined models), race (Caucasian, Asian, other), smoking status (never, former smokers quit ≥10 years, former smokers quit <10 years, current smokers <20 cigarettes/day, current smokers = 20 cigarettes/day, current smokers >20 cigarettes/day, unknown), diabetes (yes, no, missing), and BMI (continuous). The specific types of alcohol were mutually adjusted for the other types of alcohol

[c] The category is collapsed including beginning number and up

[d] Continuous ORs are expressed as per 15 g increase

[e] This zero category includes only those who did not drink that particular type of alcohol; nondrinkers of any type of alcohol were included as a separate category but data are not shown

Table 4 Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for alcohol consumption in relation to pancreatic cancer risk, by smoking status: PanScan

	Never smokers		Former smokers		Current smokers	
	Cases/controls, n	OR (95% CI)[a]	Cases/controls, n	OR (95% CI)[b]	Cases/controls, n	OR (95% CI)[b]
	584/631		304/337		376/319	
Total alcohol (g/day)						
0	250/241	1.26 (0.92–1.72)	58/55	1.03 (0.61–1.72)	55/47	0.91 (0.54–1.55)
>0 to <5	158/198	1.00	83/91	1.00	95/74	1.00
5 to <10	71/78	1.08 (0.72–1.63)	45/66	0.75 (0.45–1.26)	52/47	0.97 (0.58–1.64)
10 to <15	40/40	1.23 (0.75–2.02)	22/21	1.30 (0.65–2.61)	33/33	0.90 (0.50–1.62)
15 to <30	38/49	0.96 (0.59–1.56)	46/40	1.42 (0.82–2.46)	56/59	0.76 (0.46–1.25)
≥30	27/25	1.21 (0.66–2.22)	50/64	0.94 (0.57–1.57)	85/59	1.12 (0.69–1.81)
P-trend		0.62		0.55		0.82
OR$^c_{cont}$		0.96 (0.81–1.13)		1.04 (0.92–1.17)		1.01 (0.92–1.11)
Alcohol from beer (g/day)						
0[e]	150/161	1.00	88/95	1.00	76/62	1.00
>0 to <5	101/138	0.76 (0.53–1.10)	83/88	1.11 (0.69–1.78)	133/121	0.87 (0.56–1.36)
5 to <10	20/35[d]	0.55 (0.30–1.02)	21/21	1.49 (0.70–3.13)	41/33	1.08 (0.59–1.97)
10 to <15	–	–	9/13	1.08 (0.41–2.89)	19/19	0.82 (0.38–1.75)
≥15	14/9	1.40 (0.56–3.50)	20/27	0.96 (0.46–2.04)	48/30	1.30 (0.70–2.40)
P-trend		1.00		0.86		0.71
OR$^c_{cont}$		1.00 (0.70–1.43)		0.98 (0.75–1.28)		1.02 (0.91–1.16)
Alcohol from wine (g/day)						
0[e]	36/38	1.00	26/31	1.00	146/150	1.00
>0 to <5	155/205	0.82 (0.49–1.39)	111/122	1.11 (0.59–2.06)	117/71	1.78 (1.16–2.73)
5 to <10	49/50	1.14 (0.61–2.13)	38/33	1.13 (0.53–2.38)	21/16	1.32 (0.63–2.75)
10 to <15	23/27	0.99 (0.47–2.09)	23/22	1.15 (0.49–2.66)	6/14	0.52 (0.18–1.52)
≥15	22/23	1.11 (0.51–2.38)	23/36	0.71 (0.32–1.56)	27/14	1.77 (0.82–3.83)
P-trend		0.60		0.22		0.95
OR$^c_{cont}$		1.09 (0.78–1.53)		0.85 (0.65–1.10)		0.99 (0.78–1.26)
Alcohol from liquor (g/day)						
0[e]	132/160	1.00	66/75	1.00	47/46	1.00
>0 to <5	114/146	0.93 (0.66–1.32)	105/123	0.98 (0.63–1.54)	136/89	1.57 (0.94–2.61)
5 to <10	18/13	1.64 (0.76–3.51)	19/21	1.15 (0.55–2.39)	43/47	1.05 (0.56–1.94)
10 to <15	9/10	1.06 (0.41–2.76)	9/9	1.94 (0.66–5.69)	22/27	0.97 (0.46–2.03)
≥15	12/14	1.01 (0.44–2.31)	22/16	1.63 (0.75–3.50)	69/56	1.23 (0.69–2.21)
P-trend		0.43		0.17		0.96
OR$^c_{cont}$		0.88 (0.65–1.20)		1.18 (0.93–1.49)		1.01 (0.82–1.24)

The P values for interaction of continuous alcohol (type) by smoking status are 0.98 (total alcohol), 0.84 (beer), 0.59 (wine), and 0.52 (liquor)

[a] Adjusted for age (continuous), cohort, sex, race (Caucasian, Asian, other), diabetes (yes, no, missing), and BMI (continuous). The specific types of alcohol were mutually adjusted for the other types of alcohol. The PHS cohort and EPIC-Umea center were removed from the specific alcohol beverage analyses as alcohol type was not available

[b] Adjusted for age (continuous), cohort, gender, race (Caucasian, Asian, other), smoking (dose continuous, duration continuous), diabetes (yes, no, missing), and BMI (continuous). The specific types of alcohol were mutually adjusted for the other types of alcohol

[c] Continuous ORs are expressed as per 15 g increase

[d] The category is collapsed including beginning number and up to 15

[e] Nondrinkers of any type of alcohol were included in all analyses, but data are not shown

Our findings agree with most observational studies examining alcohol intake and pancreatic cancer [7]; only 4 of the 12 cohorts included in this pooled analysis have previously reported individual results on alcohol and pancreatic cancer [10–12]. To date, four prospective cohort studies (out of 16) observed an increase in risk with high

alcohol intake [16–18, 22]; however, no adjustment for smoking was made in one study [18], and the small number of cases ($n = 66$) in another study [17] led to unstable estimates. In four cohort studies among alcoholics, the incidence rates of pancreatic cancer were higher than those in the general population, with standardized incidence ratios (SIRs) ranging between 1.3 and 2.6 [23–26]. Those latter studies, however, could not adjust for potential confounding factors, including smoking, which could account for the excess risk observed.

A recent pooled analysis reported a significant 22% increase in risk of pancreatic cancer among those consuming ≥30 g/day vs. none [27]. In this analysis, 5 of the cohort studies were also included in our analysis but 9 others were different. Unlike this study, the increase in risk was stronger in women than in men (women, RR = 1.41, 95% CI = 1.07–1.85; men, RR = 1.12, 95% CI = 0.89–1.39), and no association was observed for the specific types of alcoholic beverages (wine, beer or spirits). However, overall the relative risk was almost identical to ours (RR = 1.23, 95% CI = 0.97–1.57, for >30 g/day vs. >0 to <5 g/day, Fig. 1). In addition, the NIH-AARP cohort study recently published findings on alcohol with 1,149 pancreatic cancer cases and observed a 45% increased risk among those consuming >3 drinks (95% CI = 1.17–1.80) and a 55% increase in risk among those consuming 6 or more drinks of alcohol a day compared to >0 to <1 drinks/day (RR = 1.55, 95% CI = 1.13–2.13, P-trend = 0.004) [22]. In that study, liquor consumption was significantly associated with risk (RR = 1.62, 95% CI = 1.24–2.10, ≥3 drinks/day vs. 0), whereas beer and wine were not. A large cohort study of women with 1,325 pancreatic cancer cases did not observe an increase in risk (RR = 1.07, 95% CI = 0.85–1.35, for 15 or more drinks/week vs. non-drinkers) [15], but the cutpoint for the highest category of alcohol intake may not have been sufficiently high to detect an increase in risk.

The two-fold increase in risk observed for high liquor intake among men is noteworthy, especially given similar findings in the NIH-AARP cohort study [22]. Although chance or confounding may explain these findings, alternative explanations are possible. For example, men reporting consuming 45 or more grams of alcohol from liquor per day may be more likely to be alcoholics than those consuming other alcoholic beverages. The observation, in this analysis, that women did not have a higher risk of pancreatic cancer with increasing liquor intake may support this explanation, as women are less likely to be alcoholics [43]. As alcoholism can lead to acute and chronic pancreatitis, the elevated risk observed may be a consequence of this condition (whether clinical or sub-clinical) as it is a well-established risk factor for pancreatic cancer [6]. Information on pancreatitis diagnosis was not available for the majority of cohorts included in this study and thus could not be included in the analysis. As alcohol intake is positively associated with a number of lifestyle factors that are linked to socioeconomic status, it is also plausible that the observed increase risk is due to confounding by an unknown risk factor that is associated with alcohol intake.

In addition to chronic pancreatitis, alternative mechanisms through which alcohol may act to increase pancreatic carcinogenesis are equally plausible. These include increased risk of diabetes type II among heavy alcohol drinkers, and metabolic effects on the inflammatory response [44]. Alcohol can influence the inflammatory response through a number of pathways, including activation of nuclear transcription factors, increased production of reactive oxidation species, activation of pancreatic stellate cells, which leads to fibrosis, and dysregulation of proliferation and apoptosis [44]. Alcohol may also act in synergy with cigarette smoke compounds to increase the inflammatory response. In this study, however, we did not observe a synergistic effect of alcohol and cigarette smoke. Based on our findings, and the literature to date, it appears unlikely that the metabolic effects of alcohol are sufficient to increase the risk of pancreatic cancer.

By combining a number of large cohort studies, we were able to pool a large number of pancreatic cancer cases to examine a broad range of alcoholic exposure and conduct analyses stratified by potential effect modifiers. All exposure data were collected prior to cancer diagnosis, avoiding any possibility of recall bias. In addition, the cohort studies in this analysis all have high follow-up rates and detailed endpoint ascertainment. The major limitation to the study is the possibility of measurement error in the exposure assessment, given that only one measurement of alcohol use was available in this analysis and that changes in alcoholic consumption might have occurred before or after the measurement. Measurement error could have led to attenuation of the true risk estimate. In addition, alcohol intake was assessed with varying questionnaires across the cohorts, each with potentially different measurement error.

In this pooled analysis, we observed no significant association for moderate to high levels of alcohol intake in relation to risk of pancreatic cancer. However, a 23% increase in risk for ≥30 g/day observed in this study was comparable to a significant 22% increase in risk reported by a recent pooled cohort study [27]. Folate intake, BMI, cigarette smoking history, and sex did not modify the overall association between alcohol intake and pancreatic cancer. Examination of different types of alcoholic beverages provided some suggestion that heavy liquor use may be associated with a higher risk of pancreatic cancer among men.

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