Alcohol consumption and pancreatic cancer: a pooled analysis in the International Pancreatic Cancer Case–Control Consortium (PanC4)

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Background: Heavy alcohol drinking has been related to pancreatic cancer, but the issue is still unsolved.
Methods: To evaluate the role of alcohol consumption in relation to pancreatic cancer, we conducted a pooled analysis of 10 case–control studies (5585 cases and 11 827 controls) participating in the International Pancreatic Cancer Case–Control Consortium. We computed pooled odds ratios (ORs) by estimating study-specific ORs adjusted

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for selected covariates and pooling them using random effects models.

Results: Compared with abstainers and occasional drinkers (<1 drink per day), we observed no association for light-to-moderate alcohol consumption (≤4 drinks per day) and pancreatic cancer risk; however, associations were above unity for higher consumption levels (OR = 1.6, 95% confidence interval 1.2–2.2 for subjects drinking ≥9 drinks per day). Results did not change substantially when we evaluated associations by tobacco smoking status, or when we excluded participants who reported a history of pancreatitis, or participants whose data were based upon proxy responses. Further, no notable differences in pooled risk estimates emerged across strata of sex, age, race, study type, and study area.

Conclusion: This collaborative-pooled analysis provides additional evidence for a positive association between heavy alcohol consumption and the risk of pancreatic cancer.

Key words: alcohol drinking, case–control studies, ethanol, pancreatic cancer, pooled analysis, risk factors

introduction

Cigarette smoking is an established risk factor for pancreatic cancer [1], but it explains only a limited proportion of all pancreatic cancers (i.e. about one in five cases) [2]. Among other factors, some aspects of diet, nutrition, and body composition—including obesity, diabetes, and possibly low intake of fruit and vegetables and high intake of (cooked) meat—have been associated with an increased pancreatic cancer risk [3–8]. Heavy alcoholic beverage consumption is a common cause of chronic pancreatitis, mainly in men [9–11], and pancreatitis is another recognized risk factor for pancreatic cancer [4, 5, 12]. Thus, heavy alcohol consumption may be associated with an increased risk of pancreatic cancer.

Most case–control studies [13–34] and at least seven cohort studies conducted in Europe [35–39] and the United States [40, 41] have found no association between alcohol drinking and the risk of pancreatic cancer, and an International Agency for Research on Cancer (IARC) Monograph working group in 2007 concluded that there was an inadequate evidence for a role of alcohol in pancreatic cancer in humans [42]. An excess risk of pancreatic cancer in heavy drinkers, particularly in Blacks, was suggested in a multicentric case–control study conducted in the United States in the 1980s [43]. Some other case–control [44–49] and cohort [50–54] studies that were able to assess alcohol consumption in more detail reported increased risk of pancreatic cancer among participants with the highest level of alcohol consumption. However, most of these studies suffered from small sample sizes and inadequate consideration of potential confounding by tobacco smoking or presence of chronic pancreatitis.

We conducted a pooled analysis of alcohol consumption and pancreatic cancer risk using data from a large series of pancreatic cancer case–control studies within the International Pancreatic Cancer Case–Control Consortium (PanC4) [55, 56]. We examined the effect of type of alcoholic beverages and evaluated whether the association between heavy alcohol intake and pancreatic cancer risk was confounded/modified by tobacco smoking or history of pancreatitis.

methods

studies

We identified 10 case–control studies of pancreatic cancer that collected data on alcohol consumption using structured questionnaires. They included a total of 5585 participants with adenocarcinoma of the exocrine pancreas and 11 827 controls [30, 32, 43, 47, 49, 57–60]. Characteristics of each study and description of the exposure variables are given in the supplemental Appendix S1 (available at *Annals of Oncology* online). For 155 cases and 150 controls in the Shanghai study [30], 63 cases in the Toronto study [58], and 474 cases and 332 controls in the Surveillance of Environmental Aspects Related to Cancer in Humans (SEARCH) study [57], a proxy respondent was interviewed.

exposure variables

Questions about alcoholic beverage consumption were generally similar across all studies. However, we conducted a careful and detailed examination of the comparability of alcohol-related questions as part of our harmonization of data from the multiple studies included in this pooled analysis. Details about alcohol consumption data for each study are included in the supplemental Appendix S1 (available at *Annals of Oncology* online).

In order to create uniform variables for alcohol consumption across all studies, we converted the beverage volume of each alcoholic beverage specified in the questionnaires into milliliters. For each type of alcoholic beverage (beer, wine, or liquor), we calculated the cumulative lifetime consumption of pure ethanol multiplying the volume of each alcoholic beverage, by the duration of consumption, and the volume percentage of pure ethanol (5% for beer, 12% for wine, and 40% for hard liquor). We then computed the lifetime number of standardized drinks by dividing the cumulative lifetime consumption of pure ethanol by 14.8 ml (i.e. the mean volume of pure ethanol per drink across all alcoholic beverage types in the 10 studies). Finally, we computed average frequency of consumption of each type of alcoholic beverage by dividing the lifetime number of standardized drinks by the corresponding duration. For total alcohol, we computed average frequency of consumption as the sum of the lifetime number of standardized drinks for each type of alcoholic beverage divided by the longest duration of consumption. When duration by type of alcoholic beverage was not available [43, 58–60], we considered the frequency of consumption only. For two studies that collected data about alcohol use at different ages [57, 59], we also computed a mean frequency of consumption and total duration as the sum of the age-specific durations. For studies that provided information for various alcoholic beverages within the same broad group (e.g. white and red wine or rice and fruit wine; dinner drinks, grappa, whiskey, cognac, and brandy) [30, 49, 57], we considered the sum of the frequencies and the longest duration of consumption within each group.

statistical analysis

To estimate the association between alcohol consumption and pancreatic cancer risk, we used a two-stage modeling approach [61]. At the first stage, we assessed the association between alcohol consumption and pancreatic cancer risk for each study by estimating the odds ratios (ORs) and the

corresponding 95% confidence interval (CI) using unconditional logistic regression models [62]. These models also included age (<45, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, ≥75 years), sex, education (≤8th grade, 9th–11th grade, 12th grade or high school graduates, some college or college graduates, ≥1 year of graduate school), race/ethnicity (non-Hispanic White, Hispanic, non-Hispanic Black, other), body mass index (BMI, <20, 20 to <25, 25 to <30, ≥30 kg/m2), history of diabetes (≥1 year before diagnosis), tobacco smoking (never smokers, smokers of products other than cigarettes, excigarette smokers with ≥10 years since quitting, excigarette smokers with 1 to <10 years since quitting, current cigarette smokers of 1 to <20 cigarettes per day, current cigarette smokers of ≥20 cigarettes per day, as well as a continuous term for number of cigarettes), and center, for multicentric studies. At the second stage of analysis, summary effect estimates were computed using random effects models [63]. The study-specific ORs were weighted by the inverse of the sum of their variance and the estimated between-study variance component. Heterogeneity between studies was evaluated using a χ^2 statistic [64]. To test for the significance of linear trends in pancreatic cancer risk across levels of different variables of alcohol consumption, we first estimated the trend in each study (by fitting a model including an ordinal variable, with values corresponding to an increasing score for each level of the variable), then we used a Wald test [61] to estimate the P value of the summary variable, in random effects model.

To investigate whether the effect of heavy alcohol consumption was homogenous in strata of selected covariates, we conducted analyses stratified by sex, age (<65, ≥65 years), tobacco smoking (ever, former, and current smokers of <20 cigarettes or of ≥20 cigarettes per day), race/ethnicity (non-Hispanic White, non-Hispanic Black), study area (North America, Europe), and source of controls (population, hospital). Heterogeneity across strata was evaluated using a χ^2 statistic [64].

We also conducted a sensitivity analysis to evaluate the influence of any one study on the effect estimates. One study at a time was excluded from the analysis model to assess the impact of that study upon the magnitude and statistical significance of the overall summary estimate.

In addition to the two-stage analysis, we conducted an aggregate analysis where data from all studies were pooled into a single large dataset for the analysis [61]. The association between alcohol consumption and pancreatic cancer risk was determined using unconditional multiple logistic regression models [62], adjusted for study and the potential confounding factors included in the study-specific models. We also included in the models the interaction terms between study and all confounding factors considered. The results were not substantially different from those obtained in the main two-stage analysis approach and therefore are not reported in detail.

results

Table 1 shows the distribution of sex, age, race, and other selected variables for the total population of 5585 pancreatic cancer cases and 11 827 controls. For both cases and controls, 57% of participants were men, whereas cases were somewhat older than controls (median: 65 years for cases, 63 years for controls). Cases reported higher education, higher BMI, and a greater proportion of current and ex-smokers, of diabetics, and of subjects with pancreatitis than controls.

ORs for pancreatic cancer associated with consumption of total alcohol and for specific alcoholic beverages are presented in Table 2. Compared with abstainers or occasional drinkers (<1 drink per day), risk estimates were near unity for up to 4 drinks per day and above unity for participants who consumed ≥9 drinks per day (OR = 1.6, 95% CI 1.2–2.2). We also

Table 1. Distribution of 5585 cases of pancreatic cancer and 11 827 controls according to sex, age, race, and other selected covariates included in the International Pancreatic Cancer Case–Control Consortium

Characteristics	Cases, $n\%$	Controls, $n\%$
Study, period [reference]		
Italy, 1991–2008 [49]	322 (5.8)	652 (5.5)
LSU, 2001–2006 (unpublished data)	69 (1.2)	158 (1.3)
Mayo Clinic, 2000–2008 [60]	1137 (20.4)	1291 (10.9)
MD Anderson, 2004–2008 [47]	874 (15.6)	790 (6.7)
Milan, 1982–1999 [32]	362 (6.5)	1549 (13.1)
NCI, 1986–1989 [43]	493 (8.8)	2146 (18.1)
SEARCH, 1983–1989 [57]	810 (14.5)	1679 (14.2)
Shanghai, 1990–1993 [30]	451 (8.1)	1552 (13.1)
Toronto, 2003–2006 [58]	540 (9.7)	313 (2.7)
UCSF, 1995–1999 [59]	527 (9.4)	1697 (14.4)
Sex		
Men	3149 (56.4)	6816 (57.6)
Women	2436 (43.6)	5011 (42.4)
Age (years)		
<45	221 (3.9)	860 (7.3)
45–49	301 (5.4)	759 (6.4)
50–54	518 (9.3)	1284 (10.9)
55–59	792 (14.2)	1690 (14.3)
60–64	932 (16.7)	1820 (15.4)
65–69	1008 (18.0)	1986 (16.8)
70–75	943 (16.9)	1862 (15.7)
≥75	870 (15.6)	1566 (13.2)
Race/ethnicity		
Non-Hispanic White	4594 (82.2)	8505 (71.9)
Hispanic	99 (1.8)	201 (1.7)
Non-Hispanic Black	304 (5.4)	1080 (9.1)
Others	584 (10.5)	1729 (14.6)
Missing	*4 (0.1)*	*312 (2.6)*
Education		
8th grade or less	1281 (22.9)	3569 (30.2)
9th–11th grade	750 (13.4)	1586 (13.4)
12th grade or high school graduate	1144 (20.5)	1981 (16.7)
Some college or college graduate	1597 (28.6)	3116 (26.4)
≥1 year of graduate school	770 (13.8)	1488 (12.6)
Missing	*43 (0.8)*	*87 (0.7)*
Body mass index (kg/m^2)		
<20	417 (7.5)	1064 (9.0)
20 to <25	2090 (37.4)	5264 (44.5)
25 to <30	2011 (36.0)	4049 (34.2)
≥30	985 (17.6)	1291 (10.9)
Missing	*82 (1.5)*	*159 (1.3)*
Tobacco smoking		
Never smokers	2041 (36.5)	5126 (43.3)
Smokers other than cigarettes	129 (2.3)	292 (2.5)
Cigarette smokers		
Current smokers (cigarettes/day)		
<20	998 (17.9)	2042 (17.3)
≥20	445 (8.0)	558 (4.7)
Ex-smokers (years since quitting)		
>10	1264 (22.6)	2547 (21.5)
≤10	618 (11.1)	1127 (9.5)
Missing	*90 (1.6)*	*135 (1.1)*

Table 1. (*Continued*)

Characteristics	Cases, *n*%	Controls, *n*%
History of diabetes		
No	4381 (78.4)	10 782 (91.2)
Yes	1127 (20.2)	974 (8.2)
Missing	*77 (1.4)*	*71 (0.6)*
History of pancreatitis[a]		
No	3825 (68.5)	9657 (81.7)
Yes	242 (4.3)	95 (0.8)
Missing	*1518 (27.2)*	*2075 (17.5)*

[a]No information was available in the Italian and Mayo Clinic study.
LSU, Louisiana State University; NCI, National Cancer Institute; SEARCH, Surveillance of Environmental Aspects Related to Cancer in Humans; UCSF, University of California, San Francisco.

considered total alcohol consumption after excluding 692 cases and 482 controls for whom information was based on proxy interview. All ORs were similar to those obtained in the overall pooled dataset, i.e. the OR for ≥9 drinks per day was 1.9 (95% CI 1.4–2.5). Results of sensitivity analyses showed that no single study unduly influenced the magnitude or the statistical significance of the summary estimates. In analyses by type of alcohol, ORs were increased for participants who consumed ≥4 drinks of wine per day (OR = 1.5; 95% CI 1.0–2.1; *P* trend 0.02), whereas no excess risk was observed for consumption of beer or hard liquor, although the data were sparse (Table 2).

A forest plot of study-specific and pooled ORs for pancreatic cancer risk associated with total alcohol consumption is presented in Figure 1. The pooled OR was 0.9 (95% CI 0.7–1.2) for 1 to <4 drinks per day, 1.2 (95% CI 1.0–1.5) for 4 to <6 drinks per day, and 1.5 (95% CI 1.2–1.8) for ≥6 drinks per day. ORs were elevated for the highest category of alcohol consumption in six studies. In the latter category, there was no evidence of between-study heterogeneity (*P* = 0.18). Results of analyses excluding participants with pancreatitis (OR = 1.4, 95% CI 1.1–1.7, for ≥6 drinks per day) and data from proxy respondents (OR = 1.6, 95% CI 1.3–1.9, for ≥6 drinks per day) were consistent with the overall results.

Additional analyses of total alcohol consumption (specifically heavy drinking, i.e. ≥6 drinks per day) were stratified by sex, age, tobacco smoking, race/ethnicity, study area, and source of controls (Table 3). The associations appeared somewhat stronger—although not significant—in Black than in White subjects. No notable or significant differences in risk estimates were observed by sex, age, study area, source of controls, or tobacco smoking. Further, no differences in risk estimates were observed by education, BMI, and history of diabetes (data not shown).

Data on duration of alcohol drinking were available in five studies only [30, 32, 47, 49, 57] and showed no consistent associations (OR = 0.9; 95% CI 0.7–1.1, for the highest duration of consumption, ≥40 years) (data not shown).

discussion

This collaborative-pooled analysis of data from the PanC4 case–control studies provides additional evidence, and more accurate quantitative estimates than previously available, on the

Table 2. Pooled ORs and corresponding 95% CIs of pancreatic cancer according to alcohol consumption in the International Pancreatic Cancer Case–Control Consortium (PanC4).

Frequency, drinks per day[a]	Cases, *n* (%)	Controls, *n* (%)	OR[b] (95% CI)
Total alcohol			
0 to <1	3587 (64.2)	7044 (59.5)	1 (Referent)
1 to <2	693 (12.4)	1580 (13.4)	1.02 (0.76–1.37)
2 to <3	434 (7.8)	1149 (9.7)	0.91 (0.73–1.15)
3 to <4	230 (4.1)	637 (5.4)	0.93 (0.69–1.26)
4 to <5	229 (4.1)	541 (4.6)	1.26 (0.99–1.61)
5 to <6	88 (1.6)	245 (2.1)	1.14 (0.86–1.50)
6 to <7	80 (1.4)	171 (1.4)	1.59 (1.16–2.20)
7 to <8	46 (0.8)	94 (0.8)	1.30 (0.81–2.09)
8 to <9	61 (1.1)	156 (1.3)	1.25 (0.74–2.10)
≥9	121 (2.2)	201 (1.7)	1.60 (1.16–2.22)
Missing	*16 (0.3)*	*9 (0.1)*	–
P value for trend			0.302
Total alcohol[c]			
0 to <1	3108 (63.5)	6698 (59.0)	1 (Referent)
1 to <2	613 (12.5)	1525 (13.4)	1.01 (0.74–1.38)
2 to <3	398 (8.1)	1105 (9.7)	0.96 (0.76–1.22)
3 to <4	194 (4.0)	621 (5.5)	0.88 (0.66–1.19)
4 to <5	205 (4.2)	536 (4.7)	1.20 (0.91–1.59)
5 to <6	76 (1.6)	243 (2.2)	1.13 (0.81–1.56)
6 to <7	75 (1.5)	170 (1.5)	1.63 (1.18–2.26)
7 to <8	44 (0.9)	93 (0.8)	1.34 (0.82–2.19)
8 to <9	56 (1.1)	153 (1.4)	1.27 (0.69–2.32)
≥9	110 (2.3)	192 (1.7)	1.86 (1.40–2.47)
Missing	*14 (0.3)*	*9 (0.1)*	–
P value for trend			0.302
Wine only[d]			
0 to <1[e]	3317 (90.8)	5805 (85.2)	1 (Referent)
1 to <4	251 (6.9)	704 (10.3)	1.18 (0.91–1.52)
≥4	87 (2.4)	307 (4.5)	1.46 (1.02–2.08)
P value for trend			0.017
Beer only[d]			
0 to <1[e]	3317 (96.7)	5805 (96.9)	1 (Referent)
1 to <4	78 (2.3)	143 (2.4)	0.81 (0.46–1.43)
≥4	34 (1.0)	46 (0.8)	0.69 (0.41–1.17)
P value for trend			0.105
Liquor only[d]			
0 to <1[e]	3317 (97.3)	5805 (96.9)	1 (Referent)
≥1	93 (2.7)	188 (3.1)	1.13 (0.84–1.52)

[a]Derived from cumulative lifetime consumption for study providing information (see 'Methods').
[b]Pooled ORs were computed using random effects models. Study-specific ORs were adjusted for age, sex, race/ethnicity, education, body mass index, history of diabetes, tobacco smoking (in categories, plus a continuous term), and center for multicentric studies.
[c]Excluding proxy interviews (692 cases and 482 controls).
[d]No information on type of alcoholic beverages was available in the NCI study.
[e]Abstainers or occasional drinkers of any kind of alcoholic beverages. OR, odds ratio; CI, confidence interval; NCI, National Cancer Institute.

association between heavy alcohol consumption and the risk of pancreatic cancer. Compared with abstainers or occasional drinkers, ORs of pancreatic cancer were at or near unity for participants who drank up to 4 drinks per day, and statistically
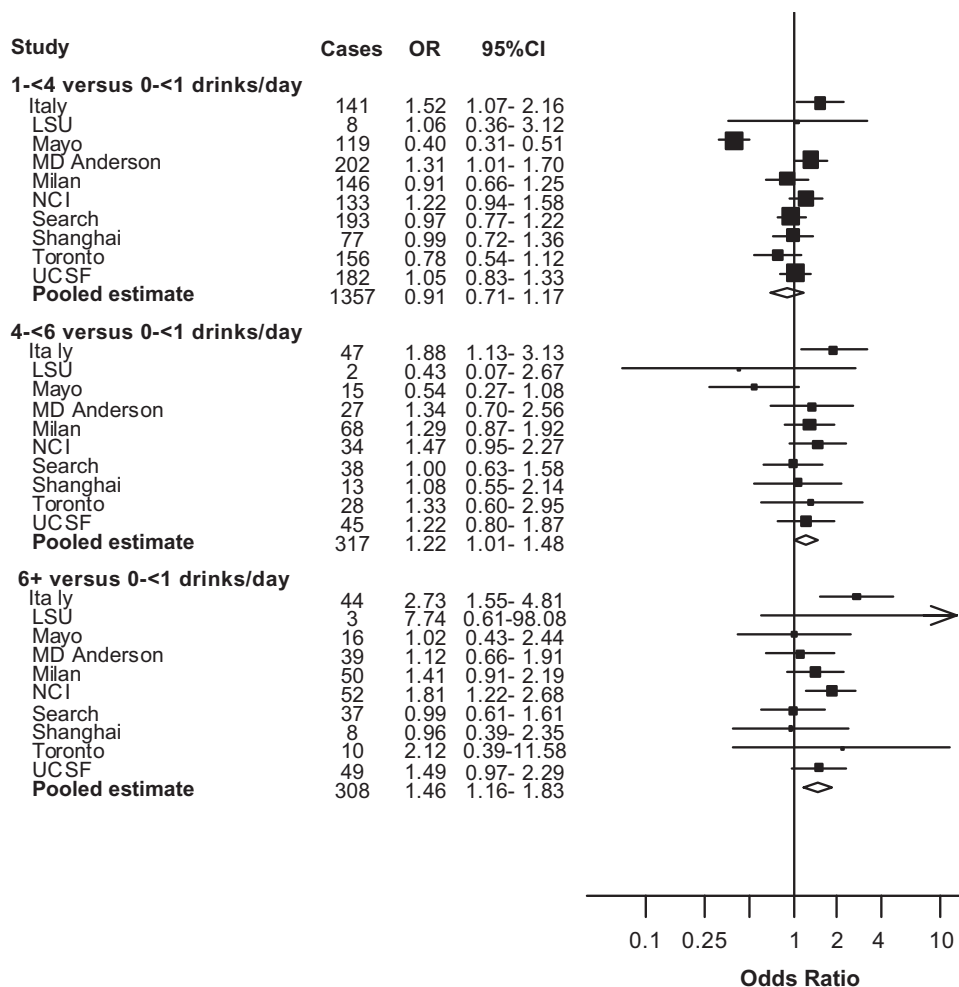
Study	Cases	OR	95%CI
1-<4 versus 0-<1 drinks/day			
Italy	141	1.52	1.07- 2.16
LSU	8	1.06	0.36- 3.12
Mayo	119	0.40	0.31- 0.51
MD Anderson	202	1.31	1.01- 1.70
Milan	146	0.91	0.66- 1.25
NCI	133	1.22	0.94- 1.58
Search	193	0.97	0.77- 1.22
Shanghai	77	0.99	0.72- 1.36
Toronto	156	0.78	0.54- 1.12
UCSF	182	1.05	0.83- 1.33
Pooled estimate	1357	0.91	0.71- 1.17
4-<6 versus 0-<1 drinks/day			
Ita ly	47	1.88	1.13- 3.13
LSU	2	0.43	0.07- 2.67
Mayo	15	0.54	0.27- 1.08
MD Anderson	27	1.34	0.70- 2.56
Milan	68	1.29	0.87- 1.92
NCI	34	1.47	0.95- 2.27
Search	38	1.00	0.63- 1.58
Shanghai	13	1.08	0.55- 2.14
Toronto	28	1.33	0.60- 2.95
UCSF	45	1.22	0.80- 1.87
Pooled estimate	317	1.22	1.01- 1.48
6+ versus 0-<1 drinks/day			
Ita ly	44	2.73	1.55- 4.81
LSU	3	7.74	0.61-98.08
Mayo	16	1.02	0.43- 2.44
MD Anderson	39	1.12	0.66- 1.91
Milan	50	1.41	0.91- 2.19
NCI	52	1.81	1.22- 2.68
Search	37	0.99	0.61- 1.61
Shanghai	8	0.96	0.39- 2.35
Toronto	10	2.12	0.39-11.58
UCSF	49	1.49	0.97- 2.29
Pooled estimate	308	1.46	1.16- 1.83

Figure 1. Study-specific and pooled odds ratios* (ORs) of pancreatic cancer according to total alcohol consumption in the International Pancreatic Cancer Case–Control Consortium. *Pooled ORs were computed using random effects models. Study-specific ORs were adjusted for age, sex, race/ethnicity, education, body mass index, history of diabetes, tobacco smoking (in categories, plus a continuous term), and center for multicentric studies. CI, confidence interval; LSU, Louisiana State University; NCI, National Cancer Institute; SEARCH, Surveillance of Environmental Aspects Related to Cancer in Humans; UCSF, University of California, San Francisco.

significantly above unity for higher intakes, with up to a 60% increased risk among extremely heavy alcohol drinkers (≥9 drinks per day). No consistent relation was observed for duration of alcohol drinking using available data. This is not surprising, since for oral cancer and other alcohol-related neoplasms, the association between duration and risk is much less consistent than that with dose [65–67].

Although the 2007 IARC Monograph Working Group concluded that there was inadequate evidence for alcohol carcinogenicity on pancreatic cancer [42], an association between heavy alcohol consumption and risk of pancreatic cancer has been reported in some case–control [43–49] and cohort [50–54] studies. An IARC Monograph Working Group in 2009 concluded that there was limited evidence for a causal association between alcohol consumption and pancreatic cancer risk [68], referring to a meta-analysis of 21 case–control and 11 cohort studies [69] that showed an overall relative risk (RR) of 0.92 for consumption of <3 drinks/day, but of 1.22 (95% CI 1.12–1.34) for higher consumption. Likewise, the 'Pooling Project of Prospective Studies of Diet and Cancer'

[70], which included 14 cohort studies for a total of 2187 incident cases, found no association up to 30 g/day of alcohol consumption (∼3 drinks/day) but a moderate positive association for the highest category of consumption (RR = 1.22, 95% CI 1.03–1.45). Moreover, in that study, it was not possible to investigate the higher consumption of alcohol (>3 drinks/day) due to the small number of heavy drinkers in most (American) cohort studies. The Pancreatic Cancer Cohort Consortium-nested case–control analysis based on 1530 pancreatic cases found no significant association between total alcohol intake and pancreatic cancer risk; and the OR was increased for the highest consumption though not significantly (OR = 1.38, 95% CI 0.86–2.23 for ≥60 g/day) [71]. However, that study did report a significant excess risk for ≥45 g/day for liquor in men (OR = 2.23, 95% CI 1.02– 4.87), but the number of subjects in the various levels of intake and analyses of type of beverages were too limited for definitive conclusions.

Our results based on a reanalysis of original data from a uniquely large pooled dataset provide additional data on

Table 3. Pooled ORs and corresponding 95% CIs of pancreatic cancer according to alcohol consumption in strata of selected covariates in the International Pancreatic Cancer Case–Control Consortium (PanC4)

	Frequency, drinks per day[a]				OR[b] (95% CI)	P value for interaction
	0 to <1 (referent)		≥6			
	Cases, *n* (%)	Controls, *n* (%)	Cases, *n* (%)	Controls, *n* (%)		
Overall	3587 (64.4)	7044 (59.6)	308 (5.5)	622 (5.3)	1.46 (1.16–1.83)	
Sex						
Men	1675 (53.4)	3077 (45.2)	283 (9.0)	590 (8.7)	1.43 (1.07–1.91)	0.708
Women	1912 (78.7)	3967 (79.2)	25 (1.0)	32 (0.6)	1.64 (0.86–3.11)	
Age (years)						
<65	1676 (60.8)	3638 (56.8)	208 (7.5)	423 (6.6)	1.55 (1.21–2.00)	0.600
≥65	1911 (68.0)	3406 (63.0)	100 (3.6)	199 (3.7)	1.37 (0.92–2.04)	
Cigarette smoking						
Never smokers	1600 (78.6)	3890 (76.0)	32 (1.6)	105 (2.1)	1.31 (0.68–2.54)	0.677
Ex-smokers	1094 (58.4)	1785 (48.6)	117 (6.2)	214 (5.8)	1.67 (1.23–2.26)	
Current smokers						
<20 cigarettes/day	560 (56.2)	958 (46.9)	76 (7.6)	172 (8.4)	1.46 (0.94–2.27)	
≥20 cigarettes/day	209 (47.2)	193 (34.6)	72 (16.3)	109 (19.5)	0.99 (0.42–2.34)	
Race/ethnicity						
Non-Hispanic White	2877 (62.8)	4747 (55.8)	259 (6.0)	475 (5.6)	1.48 (1.15–1.92)	0.523
Non-Hispanic Black	174 (57.6)	619 (57.4)	32 (10.8)	104 (9.6)	1.83 (1.02–3.28)	
Study area						
North America	2788 (68.8)	4523 (63.4)	191 (4.7)	323 (4.5)	1.32 (0.97–1.80)	0.157
Europe	374 (38.7)	1124 (39.0)	107 (11.1)	272 (9.4)	1.96 (1.25–3.09)	
Sources of controls						
Hospital	1173 (64.5)	1600 (45.8)	110 (6.1)	269 (7.7)	1.66 (0.98–2.82)	0.519
Population	2414 (64.4)	5444 (65.4)	198 (5.3)	353 (4.3)	1.37 (1.07–1.75)	

[a]Derived from cumulative lifetime consumption for study providing information (see 'Methods').
[b]Pooled ORs were computed using random effects models. Study-specific ORs were adjusted for age, sex, race/ethnicity, education, body mass index, history of diabetes, tobacco smoking (in categories, plus a continuous term), and center for multicentric studies.
OR, odds ratio; CI, confidence interval.

heavier alcohol consumption (i.e. 6–>9 drinks per day) and pancreatic cancer risk. We also were uniquely able to evaluate whether the association between (heavy) alcohol consumption and pancreatic cancer risk was modified by pancreatitis or tobacco smoking. More importantly, we were able to uniformly define the modeling of the exposure, confounding, and outcome variables [61]. Finally, our data harmonization and pooling allowed more detailed adjustment for tobacco smoking than in several individual studies and meta-analyses of alcohol and pancreatic cancer risk.

Heavy alcohol consumption is a recognized cause of chronic pancreatitis [9–11, 72], a known risk factor for pancreatic cancer. In our dataset, 242 cases and 95 controls reported a history of pancreatitis. Our results did not substantially change when we excluded these individuals from the analysis. Although several studies queried participants to ascertain physician-diagnosed acute or chronic pancreatitis and number of episodes, it is difficult to assess the validity of (self-reported) information on pancreatitis, because of the potential misclassification between the various forms of acute and chronic pancreatitis, and obstructive pancreatitis resulting from duct blockage due to the presence of a pancreatic tumor [73, 74]. To diminish the potential for reverse causation on effect estimates, pancreatitis diagnosed in the short term (at least 1 year) before diagnosis/interview was not considered.

Heavy alcohol drinking also may have a direct effect on pancreatic carcinogenesis. Acetaldehyde [75]—the main metabolite of ethanol—is a known carcinogen and the induction of pancreatic injury from fatty acid ethyl esters [12, 76] and reactive oxygen species [77] are possible mechanisms and might explain the association between heavy alcohol drinking and pancreatic cancer.

Cigarette smoking is an established risk factor for pancreatic cancer [1] and is often positively correlated with alcohol drinking. In our analyses, the association between heavy alcohol drinking and pancreatic cancer was consistently elevated among ever, former, and current (moderate and heavy) smokers. Interestingly, the magnitude of the effect was lowest among heavy current smokers, moderate for never and current moderate smokers, and greatest for ex-smokers. This result argues against the hypothesis that the excess risk among heavy drinkers is due to the correlation between heavy alcohol drinking and heavy tobacco smoking. Furthermore, in subanalyses that included studies with more detailed information about tobacco smoking (frequency, duration, years since quitting, and non-cigarette tobacco use), the magnitude of the association between alcohol consumption and pancreatic cancer risk was similar to the results that we reported for all studies. Thus, residual confounding by tobacco smoking is an unlikely explanation for the observed association between heavy

alcohol consumption and pancreatic cancer risk. Our results also show that other potential confounders such as age, sex, study area, education, BMI, and history of diabetes appear to not modify the effect of heavy alcohol consumption on pancreatic cancer risk. The association with heavy alcohol drinking was somewhat—although not significantly—stronger in Blacks than in Whites. This was previously reported in an National Cancer Institute-based study [43], which contributed about half of the Blacks cases to the present pooled analysis in PanC4.

Both hospital- and population-based controls can introduce selection bias, e.g. by inclusion or exclusion of alcohol-related diseases in hospital controls, and by lower participation of individuals with alcohol dependency in population-based studies. In PanC4, three studies [32, 49, 60] used hospital controls, one study selected controls from healthy individuals accompanying subjects to the hospital/clinic [47], and six studies [30, 43, 57–59] used general population controls. Our results were consistent regardless of the source of study controls.

Recall bias and misclassification also may have affected our results, particularly because alcohol drinking may be intentionally or unintentionally underreported by participants and proxies. However, our sensitivity analyses showed that it is unlikely that less complete information collected from proxies influenced the overall results. It is more difficult to assess whether differences in social acceptance of alcohol consumption may have influenced participants' response to alcohol questions during in person interviews. For three studies [32, 49, 59] included in the present analysis, reproducibility and validity of alcohol drinking were assessed and found satisfactory [78–80]. Although similar information was not available for other studies, results from our sensitivity analysis (i.e. excluding each study from the analyses) showed no substantial change in the pooled risk estimates.

We applied the same estimate of ethanol content for each type of alcoholic beverage across all studies. Although the ethanol content of wine and beer is relatively consistent across countries and regions in the world [75], there is a potential for variation in ethanol content from (hard) liquors. However, given the smaller number of liquor drinkers as compared with wine and beer drinkers, and little difference in the number of exclusive liquor drinkers by case–control status, this is not likely to have substantially influenced our results.

In summary, the results of this pooled analysis of case–control studies in PanC4 support a moderate increased risk of pancreatic cancer with heavy daily alcohol consumption that is in agreement with a previous pooled analysis of cohort studies [70] and a recent meta-analysis of published case–control and cohort studies [69]. Our data provide no evidence for a role of light or moderate alcohol drinking in pancreatic carcinogenesis, but rather, an increased risk only for heavy drinking, the effects being independent from those of tobacco smoking.

disclosure

The authors declare no conflict of interest.

references

1. International Agency for Research on Cancer. Tobacco smoke and involuntary smoking IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 83. Lyon, France: International Agency for Research on Cancer 2004.

2. Iodice S, Gandini S, Maisonneuve P, Lowenfels AB. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbecks Arch Surg 2008; 393: 535–545.

3. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: A Global Prospective. Washington, DC: AICR 1997.

4. Li D, Xie K, Wolff R, Abbruzzese JL. Pancreatic cancer. Lancet 2004; 363: 1049–1057.

5. Anderson KE, Mack TM, Silverman DT. Cancer of the pancreas. In Schottenfeld D, Fraumeni JF Jr (eds), Cancer Epidemiology and Prevention, 3rd edition. New York: Oxford University Press 2006; 721–762.

6. van den Brandt PA, Goldbohm RA. Nutrition in the prevention of gastrointestinal cancer. Best Pract Res Clin Gastroenterol 2006; 20: 589–603.

7. World Cancer Research Fund/American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Prospective. Washington, DC: AICR 2007.

8. Vrieling A, Verhage BA, van Duijnhoven FJ et al. Fruit and vegetable consumption and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2009; 124: 1926–1934.

9. Uomo G, Manes G. Risk factors of chronic pancreatitis. Dig Dis 2007; 25: 282–284.

10. Li J, Guo M, Hu B et al. Does chronic ethanol intake cause chronic pancreatitis?: evidence and mechanism. Pancreas 2008; 37: 189–195.

11. Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. JOP 2009; 10: 387–392.

12. Go VL, Gukovskaya A, Pandol SJ. Alcohol and pancreatic cancer. Alcohol 2005; 35: 205–211.

13. Williams RR, Stegens NL, Goldsmith JR. Associations of cancer site and type with occupation and industry from the Third National Cancer Survey Interview. J Natl Cancer Inst 1977; 59: 1147–1185.

14. MacMahon B, Yen S, Trichopoulos D et al. Coffee and cancer of the pancreas. N Engl J Med 1981; 304: 630–633.

15. Manousos O, Trichopoulos D, Koutselinis A et al. Epidemiologic characteristics and trace elements in pancreatic cancer in Greece. Cancer Detect Prev 1981; 4: 439–442.

16. 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: 463–470.

17. Wynder EL, Hall NE, Polansky M. Epidemiology of coffee and pancreatic cancer. Cancer Res 1983; 43: 3900–3906.

18. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas cancer and smoking, beverage consumption, and past medical history. J Natl Cancer Inst 1986; 76: 49–60.

19. Norell SE, Ahlbom A, Erwald R et al. Diet and pancreatic cancer: a case-control study. Am J Epidemiol 1986; 124: 894–902.

20. Voirol M, Infante F, Raymond L et al. [Nutritional profile of patients with cancer of the pancreas]. Schweiz Med Wochenschr 1987; 117: 1101–1104.

21. Farrow DC, Davis S. Diet and the risk of pancreatic cancer in men. Am J Epidemiol 1990; 132: 423–431.

22. Ghadirian P, Simard A, Baillargeon J et al. Nutritional factors and pancreatic cancer in the francophone community in Montreal, Canada. Int J Cancer 1991; 47: 1–6.

23. Jain M, Howe GR, St Louis P, Miller AB. Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. Int J Cancer 1991; 47: 384–389.

24. 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: 514–522.

25. Lyon JL, Mahoney AW, French TK, Moser R Jr. Coffee consumption and the risk of cancer of the exocrine pancreas: a case-control study in a low-risk population. Epidemiology 1992; 3: 164–170.

26. Mizuno S, Watanabe S, Nakamura K et al. A multi-institute case-control study on the risk factors of developing pancreatic cancer. Jpn J Clin Oncol 1992; 22: 286–291.

27. Kalapothaki V, Tzonou A, Hsieh CC et al. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. Cancer Causes Control 1993; 4: 375–382.

28. Zatonski WA, Boyle P, Przewozniak K et al. Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. Int J Cancer 1993; 53: 601–607.

29. Gullo L, Pezzilli R, Morselli-Labate AM. Coffee and cancer of the pancreas: an Italian multicenter study. Pancreas 1995; 11: 223–229.

30. 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: 369–376.

31. Partanen TJ, Vainio HU, Ojajarvi IA, Kauppinen TP. Pancreas cancer, tobacco smoking and consumption of alcoholic beverages: a case-control study. Cancer Lett 1997; 116: 27–32.

32. Tavani A, Pregnolato A, Negri E, La Vecchia C. Alcohol consumption and risk of pancreatic cancer. Nutr Cancer 1997; 27: 157–161.

33. Soler M, Chatenoud L, La Vecchia C et al. Diet, alcohol, coffee and pancreatic cancer: final results from an Italian study. Eur J Cancer Prev 1998; 7: 455–460.

34. Villeneuve PJ, Johnson KC, Hanley AJ, Mao Y. 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: 49–58.

35. 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: 680–687.

36. 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: 480–482.

37. Ye W, Lagergren J, Weiderpass E et al. Alcohol abuse and the risk of pancreatic cancer. Gut 2002; 51: 236–239.

38. Rohrmann S, Linseisen J, Vrieling A et al. Ethanol intake and the risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 2009; 20: 785–794.

39. Stevens RJ, Roddam AW, Spencer EA et al. Factors associated with incident and fatal pancreatic cancer in a cohort of middle-aged women. Int J Cancer 2009; 124: 2400–2405.

40. Hiatt RA, Klatsky AL, Armstrong MA. Pancreatic cancer, blood glucose and beverage consumption. Int J Cancer 1988; 41: 794–797.

41. Shibata A, Mack TM, Paganini-Hill A et al. A prospective study of pancreatic cancer in the elderly. Int J Cancer 1994; 58: 46–49.

42. International Agency for Research on Cancer. Alcohol consumption and ethyl carbamate. In IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 96. Lyon, France: International Agency for Research on Cancer 2010.

43. Silverman DT, Brown LM, Hoover RN et al. Alcohol and pancreatic cancer in blacks and whites in the United States. Cancer Res 1995; 55: 4899–4905.

44. Falk RT, Pickle LW, Fontham ET et al. Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. Am J Epidemiol 1988; 128: 324–336.

45. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. Int J Cancer 1989; 43: 415–421.

46. 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: 1016–1019.

47. Hassan MM, Bondy ML, Wolff RA et al. Risk factors for pancreatic cancer: case-control study. Am J Gastroenterol 2007; 102: 2696–2707.

48. Suzuki T, Matsuo K, Sawaki A et al. Alcohol drinking and one-carbon metabolism-related gene polymorphisms on pancreatic cancer risk. Cancer Epidemiol Biomarkers Prev 2008; 17: 2742–2747.

49. Talamini R, Polesel J, Gallus S et al. Tobacco smoking, alcohol consumption and pancreatic cancer risk: a case-control study in Italy. Eur J Cancer 2010; 46: 370–376.

50. Heuch I, Kvale G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br J Cancer 1983; 48: 637–643.

51. 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: 477–482.

52. 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: 1081–1086.

53. Heinen MM, Verhage BA, Ambergen TA et al. Alcohol consumption and risk of pancreatic cancer in the Netherlands cohort study. Am J Epidemiol 2009; 169: 1233–1242.

54. Jiao L, Silverman DT, Schairer C et al. Alcohol use and risk of pancreatic cancer: the NIH-AARP Diet and Health Study. Am J Epidemiol 2009; 169: 1043–1051.

55. The Pancreatic Cancer Case Control Consortium (PANC4). http://panc4.org/2007 (29 March 2011, date last accessed).

56. Bertuccio P, La Vecchia C, Silverman DT et al. Cigar and pipe smoking, smokeless tobacco use and pancreatic cancer: an analysis from the International Pancreatic Cancer Case-Control Consortium (PanC4). Ann Oncol 2011; 22: 1420–1426.

57. 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: 63–71.

58. Anderson LN, Cotterchio M, Gallinger S. Lifestyle, dietary, and medical history factors associated with pancreatic cancer risk in Ontario, Canada. Cancer Causes Control 2009; 20: 825–834.

59. Chan JM, Wang F, Holly EA. Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case-control study. Cancer Causes Control 2009; 20: 835–846.

60. McWilliams RR, Bamlet WR, de Andrade M et al. Nucleotide excision repair pathway polymorphisms and pancreatic cancer risk: evidence for role of MMS19L. Cancer Epidemiol Biomarkers Prev 2009; 18: 1295–1302.

61. Smith-Warner SA, Spiegelman D, Ritz J et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. Am J Epidemiol 2006; 163: 1053–1064.

62. Breslow NE, Day NE. Statistical Methods in Cancer Research. Volume I - The Analysis of Case-Control Studies. Lyon, France: IARC 1980.

63. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188.

64. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9: 1–30.

65. Goldstein BY, Chang SC, Hashibe M. Alcohol consumption and cancers of the oral cavity and pharynx from 1988 to 2009: an update. Eur J Cancer Prev 2010; 19: 431–465.

66. Zambon P, Talamini R, La Vecchia C et al. Smoking, type of alcoholic beverage and squamous-cell oesophageal cancer in northern Italy. Int J Cancer 2000; 86: 144–149.

67. Purdue MP, Hashibe M, Berthiller J et al. Type of alcoholic beverage and risk of head and neck cancer–a pooled analysis within the INHANCE Consortium. Am J Epidemiol 2009; 169: 132–142.

68. Secretan B, Straif K, Baan R et al. A review of human carcinogens-Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009; 10: 1033–1034.

69. Tramacere I, Scotti L, Jenab M et al. Alcohol drinking and pancreatic cancer risk: a meta-analysis of the dose-risk relation. Int J Cancer 2101; 126: 1474–1486.

70. Genkinger JM, Spiegelman D, Anderson KE et al. Alcohol intake and pancreatic cancer risk: a pooled analysis of fourteen cohort studies. Cancer Epidemiol Biomarkers Prev 2009; 18: 765–776.

71. Michaud DS, Vrieling A, Jiao L et al. Alcohol intake and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium (PanScan). Cancer Causes Control 2010; 21: 1213–1225.

72. Kristiansen L, Gronbaek M, Becker U, Tolstrup JS. Risk of pancreatitis according to alcohol drinking habits: a population-based cohort study. Am J Epidemiol 2008; 168: 932–937.

73. Karlson BM, Ekbom A, Josefsson S et al. The risk of pancreatic cancer following pancreatitis: an association due to confounding? Gastroenterology 1997; 113: 587–592.

74. Talamini G, Bassi C, Falconi M et al. Early detection of pancreatic cancer following the diagnosis of chronic pancreatitis. Digestion 1999; 60: 554–561.

75. International Agency for Research on Cancer. Re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide (part two). In IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 71. Lyon, France: International Agency for Research on Cancer 1999.

76. Criddle DN, Raraty MG, Neoptolemos JP et al. Ethanol toxicity in pancreatic acinar cells: mediation by nonoxidative fatty acid metabolites. Proc Natl Acad Sci U S A 2004; 101: 10738–10743.

77. Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. Nat Rev Cancer 2007; 7: 599–612.

78. Salvini S, Hunter DJ, Sampson L et al. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol 1989; 18: 858–867.

79. D'Avanzo B, La Vecchia C, Katsouyanni K et al. Reliability of information on cigarette smoking and beverage consumption provided by hospital controls. Epidemiology 1996; 7: 312–315.

80. Ferraroni M, Decarli A, Franceschi S et al. Validity and reproducibility of alcohol consumption in Italy. Int J Epidemiol 1996; 25: 775–782.