No association between alcohol consumption and pancreatic cancer even among individuals genetically susceptible to the carcinogenicity of alcohol

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Inconsistent results have been reported for the association between alcohol use and pancreatic cancer, particularly at low levels of alcohol consumption. Individuals genetically susceptible to the carcinogenic effect of alcohol might have higher pancreatic cancer risk after drinking alcohol. The current study investigated the association between alcohol use and pancreatic cancer with 419 pancreatic cancer cases and 963 controls recruited by a hospital-based case–control study in Taiwan. Gene-environment interaction between alcohol use and polymorphisms of two ethanol-metabolizing genes, ADH1B and ALDH2, on pancreatic risk was evaluated. Our results showed no significant association between alcohol drinking and an increased pancreatic cancer risk, even at high levels of alcohol consumption. Even among those genetically susceptible to the carcinogenic effect of alcohol (carriers of ADH1B*2/*2 (fast activity) combined with ALDH2*1/*2 (slow activity) or ALDH2*2/*2 (almost non-functional)), no significant association between alcohol use and pancreatic cancer was observed. Overall, our results suggested that alcohol drinking is not a significant contributor to the occurrence of pancreatic cancer in Taiwan.

Pancreatic cancer is a highly lethal cancer with a very low survival rate (5-year survival rate = 9%)1. During 1990 to 2017, the worldwide incidence of pancreatic cancer increased from 5.0 per 100,000 person-years to 5.7 per 100,000 person years, with approximately 448,000 incident cases occurring in 20172. Cigarette smoking, diabetes, and obesity are the three established risk factors of pancreatic cancer. The percentages of global pancreatic deaths attributed to smoking, diabetes, and obesity were estimated to be 25.9%, 9.3%, and 5.0%, respectively for men, and 16.1%, 8.6%, and 7.4%, respectively, for women2. Other factors showing strong positive associations

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A previous case–control study by Kanda et al. from Japan with 160 cases and 1,600 controls showed that the highest pancreatic cancer risk was observed among ever drinkers who carry the ADH1B*2/*2 (fast activity) genotype combination with ALDH2*1/*1 (slow activity) or ALDH2*2/*2 (almost non-functional) 19. Individuals with these genotype combinations can generate acetaldehyde rapidly after drinking alcohol but are slow at metabolizing acetaldehyde to non-carcinogenic acetate and may thus have a higher susceptibility to the carcinogenic effect of alcohol. Because the study by Kanda et al. has been the only study examining the combined effect of ADH1B and ALDH2 polymorphisms on the association between alcohol drinking and pancreatic cancer with a relatively small case sample size (n = 160), the current study aimed to investigate this topic with 419 pancreatic cancer cases and 963 controls recruited from a hospital in Taiwan, where the prevalence of ALDH2*2 carriers is the highest in the world (~ 50%).

### Results

The current analysis included 419 pancreatic cancer cases and 963 controls with a participation rate of 80% for the cases and 81% for the controls. Ninety percent of the cases were interviewed within 6 months of the pancreatic cancer diagnosis (82% within 3 months and 88% between 3–6 months). The study used frequency matching by age and sex for control selection; however, because of the ongoing recruitment of study subjects, the frequency matching process has not been completed, resulting in the imbalanced distributions of age and sex between the cases and the controls. Compared to the controls, cases had an older average age, a lower percentage of women, and a lower percentage of individuals with at least a college education (Table 1).

| Characteristics     | Cases N = 419 n (%) | Controls N = 963 n (%) | P-value* |
|---------------------|---------------------|------------------------|----------|
| **Age (years)**     |                     |                        |          |
| Mean (SE)           | 63.4 (0.5)          | 58.3 (0.4)             | <0.0001  |
| **Sex**             |                     |                        |          |
| Men                 | 237 (56.6)          | 408 (42.4)             | <0.0001  |
| Women               | 182 (43.4)          | 555 (57.6)             |          |
| **Education**       |                     |                        |          |
| ≤ Junior high       | 199 (47.5)          | 259 (26.9)             | <0.0001  |
| High school/technical school | 119 (28.4) | 252 (26.1) |           |
| College             | 86 (20.5)           | 354 (36.8)             |          |
| Graduate school     | 15 (3.6)            | 98 (10.2)              |          |

Table 1. Demographic characteristics of the pancreatic cancer patients and control subjects. N number, SE standard error. *P-values were generated using T-tests (for continuous variables) or chi-squared tests (for categorical variables).
No significant association was observed between pancreatic cancer and the status, frequency, or level of alcohol drinking (Table 2). In addition, the association between alcohol use and pancreatic cancer did not differ significantly by the cigarette smoking status (Table 3).

The polymorphisms of ADH1B and ALDH2 showed no significant associations with pancreatic cancer risk (Table 4). No significant association between alcohol use and pancreatic cancer was observed after stratification by the genotypes of ADH1B or ALDH2 (Table 5) or by the combinations of ADH1B and ALDH2 genotypes (Table 6).

**Table 2.** The association between alcohol drinking and pancreatic cancer risk. CI confidence interval, N number, OR odds ratio. *OR and 95% CI were calculated using unconditional logistic regression, adjusted for sex, age, education, cigarette smoking (pack-years), oral hygiene score, vegetable consumption, allergy, diabetes/glucose intolerance and BMI at two years before the pancreatic cancer diagnosis for the cases or before the interview date for the controls.

| Alcohol consumption | Cases N=419 n (%) | Controls N=963 n (%) | OR (95% CI)* |
|---------------------|------------------|----------------------|--------------|
| **Drinking status** |                  |                      |              |
| Never               | 152 (36.3)       | 329 (34.2)           | Reference    |
| Occasional          | 172 (41.0)       | 486 (50.5)           | 0.82 (0.60–1.11) |
| Former regular      | 34 (8.1)         | 60 (6.2)             | 0.74 (0.42–1.31) |
| Current regular     | 61 (14.6)        | 88 (9.1)             | 1.03 (0.63–1.68) |
| **Frequency**       |                  |                      |              |
| Never               | 152 (36.3)       | 329 (34.2)           | Reference    |
| Occasional          | 172 (41.0)       | 486 (50.5)           | 0.82 (0.60–1.11) |
| Monthly             | 6 (1.4)          | 13 (1.3)             | 0.94 (0.31–2.84) |
| Weekly              | 21 (5.0)         | 53 (5.5)             | 0.57 (0.29–1.12) |
| Daily               | 55 (13.1)        | 24 (7.7)             | 0.94 (0.56–1.57) |
| Unknown             | 13 (3.1)         | 13 (0.8)             | –            |
| **Level**           |                  |                      |              |
| Never               | 152 (36.3)       | 329 (34.2)           | Reference    |
| Occasional          | 172 (41.0)       | 486 (50.5)           | 0.82 (0.60–1.11) |
| Light               | 44 (10.5)        | 93 (9.7)             | 0.67 (0.40–1.13) |
| Moderate            | 6 (1.4)          | 16 (1.7)             | 0.46 (0.15–1.39) |
| Heavy               | 24 (5.7)         | 26 (2.7)             | 1.17 (0.57–2.38) |
| Unknown             | 21 (5.0)         | 13 (1.4)             | –            |

**Discussion**

Our results did not support the association between alcohol drinking and an increased pancreatic cancer risk, even at high levels of alcohol consumption. Even among those genetically susceptible to the carcinogenic effect of alcohol, no significant association between alcohol use and pancreatic cancer was observed.

Consistent with results from previous studies, our study also showed no association between low levels of alcohol use and pancreatic cancer; however, in contrary to the findings of previous studies, our study found no association between high levels of alcohol use and pancreatic cancer. In a pooled analysis combining data of 21 cohorts (n=4,211,129) from 19 prospective studies, Wang et al. reported that high level of alcohol consumption (≥ 24 g per day) was associated with an elevated pancreatic cancer risk (relative risk (RR) = 1.15, 95% CI 1.06–1.25), while no significant association was observed for low (< 12 g per day) and moderate (12–23.9 g per day) levels of alcohol consumption10. Genkinger et al. also performed a pooled analysis with 14 cohort studies (n = 862,664) and reported a 1.2 times increase in pancreatic cancer risk comparing those that drank ≥ 30 g of alcohol per day to those that drank 0 g (RR = 1.22, 95% CI 1.03–1.45) 8. Lucenteforte et al. performed a pooled analysis with 5,585 cases and 11,827 controls from 10 case–control studies, and showed a 1.6 times increase in pancreatic cancer risk for heavy drinking of ≥ 9 drinks per day (OR = 1.6, 95% CI 1.2–2.2), while light to moderate drinking (≤ 4 drinks/day) showed no significant association with pancreatic cancer9. A major reason for the non-significant finding in our study might be due to the low percentages of heavy drinkers (5.7% among cases and 2.7% among controls). Given our sample size of heavy drinkers, we calculated that our study has a power = 0.80 to detect an OR of 2.3, and a low statistical power of 0.07, 0.1, and 0.34 to detect a RR or OR of 1.15, 1.22, 1.6, respectively, reported by the previous studies8–10. Nevertheless, the low percentages of heavy alcohol drinkers suggested that heavy alcohol drinking is less likely to contribute the development of pancreatic cancer in our study population.

Only one previous study by Kanda et al. evaluated the influence of ADH1B and ALDH2 polymorphisms on the association between alcohol drinking and pancreatic cancer19. Consistent with that study, our results also showed no independent association between the polymorphisms of ADH1B and ALDH2 and pancreatic cancer risk. However, in contrast to their findings showing the strongest positive association between alcohol and pancreatic cancer among individuals with the combination of ADH1B*2/*2(fast activity) and ALDH2*1/*2(slow activity) or
### Table 3. The association between alcohol drinking and pancreatic cancer risk stratified by cigarette smoking.

| Alcohol consumption | Cases n (%) | Controls n (%) | OR (95% CI) | Cases n (%) | Controls n (%) | OR (95% CI) |
|---------------------|------------|----------------|-------------|------------|----------------|-------------|
|                      | Never smokers | Ever smokers     |              |            |                |              |
| Drinking Status      |             |                 |              |            |                |              |
| Never                | 122 (47.8) | 299 (40.8) | Reference   | 30 (18.3)  | 30 (13.8) | Reference  |
| Occasional           | 113 (44.3) | 397 (53.2) | 0.83 (0.59–1.17) | 59 (36.0)  | 89 (41.0) | 0.79 (0.38–1.63)  |
| Former regular       | 7 (2.8)    | 16 (2.1)    | 1.23 (0.45–3.41) | 27 (16.5)  | 44 (20.3) | 0.65 (0.28–1.50)  |
| Current regular      | 13 (5.1)   | 34 (4.6)    | 1.00 (0.44–2.23) | 48 (29.3)  | 54 (24.9) | 0.98 (0.46–2.12)  |
|                       |            |              |             |            |                |              |
| Frequency             |             |                 |              |            |                |              |
| Never                | 122 (47.8) | 299 (40.8) | Reference   | 30 (18.3)  | 30 (13.8) | Reference  |
| Occasional           | 113 (44.3) | 397 (53.2) | 0.83 (0.59–1.17) | 59 (36.0)  | 89 (41.0) | 0.79 (0.38–1.64)  |
| Monthly              | 5 (2.0)    | 8 (1.1)    | 2.08 (0.59–7.34) | 1 (0.6)    | 5 (2.5)    | 0.16 (0.02–1.66)  |
| Weekly               | 3 (1.2)    | 18 (2.4)    | 0.49 (0.13–1.89) | 18 (11.0)  | 35 (16.1) | 0.60 (0.25–1.49)  |
| Daily                | 7 (2.8)    | 20 (2.7)    | 0.89 (0.31–2.60) | 48 (29.3)  | 54 (24.9) | 0.94 (0.43–2.03)  |
| Unknown              | 5 (2.0)    | 4 (0.5)    | –             | 8 (4.9)    | 4 (1.8)    | –              |
|                       |            |              |             |            |                |              |
| Level                |             |                 |              |            |                |              |
| Never                | 122 (47.8) | 299 (40.8) | Reference   | 30 (18.3)  | 30 (13.8) | Reference  |
| Occasional           | 113 (44.3) | 397 (53.2) | 0.83 (0.59–1.17) | 59 (36.0)  | 89 (41.0) | 0.77 (0.37–1.61)  |
| Light                | 10 (3.9)   | 32 (4.3)    | 0.89 (0.37–2.13) | 34 (20.7)  | 61 (28.1) | 0.56 (0.25–1.25)  |
| Moderate             | 1 (0.4)    | 5 (0.7)    | 0.82 (0.09–7.95) | 5 (3.0)    | 11 (5.1)   | 0.38 (0.10–1.49)  |
| Heavy                | 2 (0.8)    | 7 (0.9)    | 0.75 (0.13–4.20) | 22 (13.4)  | 19 (8.8)   | 1.36 (0.53–3.51)  |
| Unknown              | 7 (2.8)    | 6 (0.8)    | –             | 14 (8.5)   | 7 (3.2)    | –              |

\[ P\text{-interaction}=0.74 \]

\[ P\text{-interaction}=0.34 \]

\[ P\text{-interaction}=0.90 \]

Table 4. The association between ALDH2 rs671 and ADH1B rs1229984 and pancreatic cancer risk. CI confidence interval, N number, OR odds ratio. a OR and 95% CI were calculated using unconditional logistic regression, adjusted for sex, age, education, cigarette smoking (pack-years), oral hygiene score, vegetable consumption, allergy, diabetes/glucose intolerance and BMI at two years before the pancreatic cancer diagnosis for the cases or before the interview date for the controls.

### Table 4

| ADH1B rs1229984 | Cases n (%) | Controls n (%) | OR (95% CI) |
|-----------------|-------------|----------------|-------------|
| TT (*2/*2) (Fast) | 208 (51.9)  | 502 (54.6) | Referent    |
| CT (*1/*2)      | 156 (38.9)  | 334 (36.4) | 1.11 (0.84–1.48) |
| CC (*1/*1) (Slow) | 37 (9.2)   | 83 (9.0)    | 1.20 (0.74–1.94) |

| ALDH2 rs671 | Cases n (%) | Controls n (%) | OR (95% CI) |
|-------------|-------------|----------------|-------------|
| GG (*1/*1) (Normal) | 193 (47.2) | 450 (47.9) | Referent    |
| AG (*1/*2)   | 187 (45.7)  | 407 (43.3) | 1.18 (0.90–1.56) |
| AA (*2/*2) (Non-functional) | 29 (7.2) | 83 (8.8) | 0.75 (0.44–1.25) |

| ADH1B rs1229984 + ALDH2 rs671 | Cases n (%) | Controls n (%) | OR (95% CI) |
|-------------------------------|-------------|----------------|-------------|
| Group 1: Fast ADH1B (*2/*2) + normal ALDH2 (*1/*1) | 101 (25.1) | 233 (25.6) | Referent    |
| Group 2: Fast ADH1B (*2/*2) + slow/non-functional ALDH2 (*1/*2 + *2/*2) | 107 (26.7) | 266 (29.2) | 0.98 (0.68–1.42) |
| Group 3: Slow ADH1B (*1/*1 + *1/*2) + normal ALDH2 (*1/*1) | 89 (22.2) | 203 (22.3) | 1.00 (0.67–1.48) |
| Group 4: Slow ADH1B (*1/*1 + *1/*2) + slow/non-functional ALDH2 (*1/*2 + *2/*2) | 104 (25.9) | 210 (23.0) | 1.23 (0.84–1.79) |
Our results found no significant association between alcohol drinking and pancreatic cancer regardless of the genotype combinations of ADH1B and ALDH2. Although chance finding could not be ruled out to explain the discrepant results between the two studies, a likely reason may still be the low percentage of heavy alcohol users in our study population. In the study by Kanda et al. where higher level of alcohol drinking was associated with increased pancreatic cancer risk, their sample included a higher proportion of heavy alcohol users than our study.

**Table 5.** The association between alcohol drinking and pancreatic cancer risk stratified by the genotypes of ADH1B or ALDH2. CI confidence interval, N number, OR odds ratio. *OR and 95% CI were calculated using unconditional logistic regression, adjusted for sex, age, education, cigarette smoking (pack-years), oral hygiene score, vegetable consumption, allergy, diabetes/glucose intolerance and BMI at two years before the pancreatic cancer diagnosis for the cases or before the interview date for the controls.

| Genotype  | Never | Occasional | Former regular | Current regular |
|-----------|-------|------------|----------------|-----------------|
| ADH1B rs1229984 | 81 (38.9) | 175 (34.9) | 65 (33.7) | 138 (33.1) |
| RS1229984 | 241 (48.0) | 79 (38.0) | 48 (9.6) | 48 (9.6) |
| OR (95% CI) | 0.74 (0.48–1.14) | 0.70 (0.33–1.49) | 0.94 (0.47–1.88) | 1.11 (0.53–2.32) |
| P-interaction | 0.39 |

| Genotype  | Never | Occasional | Former regular | Current regular |
|-----------|-------|------------|----------------|-----------------|
| ALDH2 rs671 | 81 (38.9) | 175 (34.9) | 65 (33.7) | 138 (33.1) |
| RS671 | 241 (48.0) | 79 (38.0) | 48 (9.6) | 48 (9.6) |
| OR (95% CI) | 0.73 (0.47–1.13) | 0.70 (0.33–1.44) | 0.80 (0.31–2.10) | 1.11 (0.53–2.32) |
| P-interaction | 0.15 |

**ALDH2*2/*2(almost non-functional)**

Although chance finding could not be ruled out to explain the discrepant results between the two studies, a likely reason may still be the low percentage of heavy alcohol users in our study population. In the study by Kanda et al. where higher level of alcohol drinking was associated with increased pancreatic cancer risk, their sample included a higher proportion of heavy alcohol users than our study.
alcohol drinking was defined as ≥ 30 g of alcohol per day. 22.5% of the cases and 15.9% of the controls met this definition, whereas in our study population only 7.2% of the cases and 4.1% of the controls met this definition. Overall, our results suggested that in a study population with low percentage of heavy alcohol users, genetic susceptibility to carcinogenicity of alcohol alone is insufficient to increase pancreatic cancer risk.

This study has several limitations. It is difficult to know whether the cases and controls in a hospital-based case–control study are from the same source population. In particular, the representativeness of the control subjects may be questionable. The percentages of ever alcohol users (occasional + regular) in our study were 80% for men and 55.5% for women, which were a little higher than the percentage of ever drinkers (70% for men and 45.3% for women) recorded by the 2013 national health survey. This could have biased our results on the association between alcohol use and pancreatic cancer towards the null. The 2013 national health survey did not record the level of alcohol use; therefore, we could not access the potential bias for heavy alcohol use in our study. Another limitation is that cases might have ruminated more about alcohol use than the controls, biasing the results away from the null. Finally, due to the differences in alcohol use prevalence and behaviors, our results may not be generalizable to populations in other countries. Our results only suggested that alcohol is not a major contributor to the occurrence of pancreatic cancer in Taiwan.

The major strength of the current study is that it is one of the few studies that assessed the combined impact of ADH1B and ALDH2 polymorphisms on the association between alcohol use and pancreatic cancer. It allowed us to show that even among individuals that are genetically susceptible to the carcinogenic effect of alcohol, alcohol use was not associated with pancreatic cancer risk.

In conclusion, our study did not support an association between alcohol use and pancreatic cancer even after considering the level of alcohol use and the influence of ADH1B and ALDH2 polymorphisms.

### Methods

The contents and the execution of the current study received approval from institutional review boards of the National Cheng Kung University Hospital and the National Health Research Institutes. Every potential study participant was informed about the details and the potential risk of participating in the study. Those who agreed to join the study were asked to provide a signed informed consent. The study was conducted according to the guidelines and the regulations set by the institutional review boards of the National Cheng Kung University Hospital and the National Health Research Institutes.

| Ethanol metabolism group | Group 1 Fast ADH1B (*2/*2) + Normal ALDH2 (*1/*1) | Group 2 Fast ADH1B (*2/*2) Slow/non-functional ALDH2 (*1/*2 + *2/*2) | Group 3 Slow ADH1B (*1/*1 + *1/*2) Normal ALDH2 (*1/*1) | Group 4 Slow ADH1B (*1/*1 + *1/*2) Slow/non-functional ALDH2 (*1/*2 + *2/*2) |
|--------------------------|-----------------------------------------------|------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| Alcohol consumption*     | Ca/Co OR (95% CI)* | Ca/Co OR (95% CI)* | Ca/Co OR (95% CI)* | Ca/Co OR (95% CI)* |
| All head and neck cancer | Never 32/72 Referent 49/101 Referent 22/51 Referent 43/84 Referent | Occasional 44/107 0.97 (0.49–1.92) 35/133 0.46 (0.24–0.86) 39/123 0.83 (0.38–1.85) 45/103 1.12 (0.59–2.14) | Former regular 8/22 0.44 (0.13–1.51) 11/16 0.89 (0.30–2.60) 6/8 0.98 (0.20–4.74) 7/9 0.73 (0.18–2.98) | Current regular 17/32 0.78 (0.27–2.31) 12/16 1.18 (0.42–3.34) 22/21 1.49 (0.47–4.67) 9/14 1.37 (0.42–4.50) | P-interaction = 0.20 |
**Subject recruitment.** Recruitment of the study subjects was performed by an ongoing case–control study of pancreatic cancer at the National Cheng Kung University Hospital. Recruitment of the pancreatic cancer cases took place at the Department of General Surgery or the Division of Hemato-Oncology, Department of Internal Medicine. Eligible cases were those with: (1) diagnosis of pancreatic ductal adenocarcinoma; (2) no cancer history prior to the diagnosis of pancreatic cancer; (3) age ≥ 20 years; and (4) the capability to comprehend the contents of the study and give informed consent. Recruitment of the controls was conducted at the Department of Family Medicine. The eligible controls were those who: (1) visited the hospital for vaccination, routine physical examination, or for minor illnesses (e.g. common cold, headache) unrelated to cigarette smoking or metabolic diseases (diabetes, hypertension, hyperlipidemia); (2) had no history of cancer; (3) were aged ≥ 20 years; and (4) were able to understand the contents of the study and give informed consent. The current study analyzed data of subjects recruited from November 19, 2013 to January 21, 2020.

**In-person interview.** In-person interview was conducted to collect data on alcohol use from each study subject. Each participant was first asked whether they ever drank any alcohol with four possible responses: never, once or twice, yes but only occasional at special events, and yes for regular drinking. Regular alcohol drinkers were further asked the followings: (1) whether they had quit drinking for more than 6 months with positive responders defined as former regular alcohol drinkers; (2) type of alcohol consumed including beer, wine, and liquor; and (3) frequency and the volume of alcohol drinking. Data on potential confounders in the association between alcohol use and pancreatic cancer were also collected. These included: (1) demographic characteristics, including age, sex, and education; (2) lifestyle habits, including use of cigarettes and intake of vegetables; (3) medical history regarding allergy and diabetes/glucose intolerance; (4) habits of oral hygiene, including regular dental visits, frequency of tooth brushing, and use of dental floss; and (5) height and weight two years prior to the diagnosis of pancreatic cancer for the cases or before the date of interview for the controls. We collected data on weight two years prior to the diagnosis of pancreatic cancer for the cases to minimize reverse causation in the association between body mass index (BMI) and pancreatic cancer.

**Collection and processing of DNA samples.** To obtain DNA, all subjects were asked to provide blood samples collected in vacutainer tubes containing EDTA (lavender-top) or buccal swab samples obtained by gently brushing the buccal mucosa with FLOQSwabs (Copan Flock Technologies, Brescia, Italy). Buffy coat was separated from the blood by centrifugation before DNA extraction. Commercially available DNA purification kit was used to extract genomic DNA from the buffy coat and the buccal swab samples. DNA samples were kept in a −80 °C refrigerator until ready for genotyping.

**Genotyping.** ADH1B rs1229984 and ALDH2 rs671 were genotyped for each study subject using Taqman-based allelic discrimination method on an Applied Biosystems 7500 Real-Time Polymerase Chain Reaction System (Applied Biosystems, Foster City, CA).

**Statistical analysis.** T-test was performed to compare the mean age between cases and the controls. The differences in the distributions of sex and education levels between cases and controls were evaluated using chi-squared test. The odds ratios (OR) and 95% confidence interval (CI) for estimating the association between alcohol use and pancreatic cancer was generated by unconditional logistic regression analysis, adjusted for age, sex, educational level, cigarette smoking, oral hygiene, vegetable intake, history of allergy, history of diabetes/glucose intolerance, and BMI. Alcohol use was evaluated in several ways: (1) by status, including never, occasional, former regular, and current regular; (2) by frequency, including monthly, weekly, and daily; (3) by level, with light drinking defined as < 1 drink/day (14 g of pure alcohol) for women and < 2 drinks/day for men, moderate drinking defined as 1–3 drinks/day for women and 2–4 drinks/day for men, and heavy drinking as > 3 drinks/day for women and > 4 drinks/day for men. The total grams of pure alcohol were calculated according to the frequency and the volume of alcohol consumption and the types of alcoholic beverage consumed. The grams/day of pure alcohol was first calculated for each beverage type with the formula: total volume per day × alcohol content (5% for beer, 13% for wine, and 40% for liquor) × density of ethanol (0.798 g/ml). The grams/day of alcohol for the different beverage types were then added together to generate the total grams/day of pure alcohol.

The association between alcohol use and pancreatic cancer was further stratified by the use of cigarettes to evaluate whether cigarette use may modify the association between alcohol and pancreatic cancer. The difference between the smoking strata was evaluated by comparing the logistic regression model with a product term (alcohol × cigarette) to the model without the product term using the log-likelihood ratio test.
(alcohol × ADH1B rs1229984 or alcohol × ALDH2 rs671 or alcohol × ethanol-metabolizing group) to the model without the product term using the log-likelihood ratio test.

**Data availability**

All data generated or analyzed during this study are included in this published article.

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**Author contributions**

Study concepts: Y.S.S., L.T.C., J.S.C. Data acquisition: all authors. Data analysis: J.S.C. Data interpretation: all authors. Manuscript preparation: Y.S.S., L.T.C., C.H.W., J.S.C. Final approval of the manuscript: all authors.

**Competing interests**

The authors declare no competing interests.

**Additional information**

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