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ORIGINAL PAPER

Lifetime alcohol intake and pancreatic cancer incidence and survival: findings from the Melbourne Collaborative Cohort Study

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Abstract

Purpose Pancreatic cancer has one of the worst prognoses with 5-year survival below 10%. There is some evidence that alcohol consumption might increase the risk of pancreatic cancer. We examined associations of pre-diagnostic alcohol intake with (i) incidence of pancreatic cancer, and (ii) overall survival following pancreatic cancer.

Methods Usual alcohol intake was estimated at recruitment in 1990–1994 for 38,472 participants in the Melbourne Collaborative Cohort Study using recalled frequency and quantity of beverage-specific intake for 10-year periods from age 20. Pancreatic cancer incidence (C25 according to International Classification of Diseases for Oncology) and vital status were ascertained through to 30 September 2015. Cox regression was performed to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for associations with lifetime, age 20–29, and baseline alcohol intakes.

Results By the end of follow-up (average 20.2 years), 239 incident cases of pancreatic cancer were diagnosed, of which 228 had died. No evidence of an association was observed between alcohol intake and risk of pancreatic cancer. Higher lifetime alcohol intake was associated with lower overall survival following a diagnosis of pancreatic cancer (mortality HR 1.09 per 10 g/day increment, 95% CI 1.00–1.19; p value = 0.04). A similar finding was observed for age 20–29 intake (HR 1.09 per 10 g/day increment, 95% CI 1.02–1.18; p value = 0.01) but not with baseline intake.

Conclusions We observed an association between lower alcohol use from an early age and improved survival following pancreatic cancer, but this finding needs to be confirmed by other studies.

Keywords Alcohol intake · Incidence · Pancreatic cancer · Survival

Abbreviations

CI	Confidence interval
HR	Hazard ratio
MCCS	Melbourne Collaborative Cohort Study

Introduction

Pancreatic cancer is frequently diagnosed in late stages and has one of the lowest 5-year survival rates (~8.5%), making prevention paramount [1]. The absence of specific symptoms coupled with no known early marker for screening is one of the main reasons why diagnosis is often made when the

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tumor or metastases are already locally advanced, despite advances in diagnostic techniques using high-resolution imaging [2]. Furthermore, prognosis continues to remain poor even with evolving new treatment regimens using chemotherapeutic agents such as gemcitabine [3], FOLFIRINOX [4], and nab-paclitaxel [5]. For instance, pancreatic ductal adenocarcinoma is the fifth leading cause of cancer-related death in Western countries [6]. This dilemma is set to aggravate further in the next decade with the incidence of pancreatic cancer set to rise globally, including in the industrialized nations [7, 8].

Ethanol in alcoholic beverages and its metabolite acetaldehyde are carcinogens causally linked to several cancers [9]. There is some evidence that an alcohol intake of 30 g/day or more is associated with a small increased risk of pancreatic cancer [10]. The recently updated meta-analyses of the World Cancer Research Fund point to no clear linear association between alcohol use and risk of pancreatic cancer but are suggestive of an increased risk limited to those consuming more than about three drinks a day [11]. Similarly, it is not established yet whether limiting pre-diagnostic alcohol use has a favorable impact on survival following a diagnosis of pancreatic cancer.

Alcohol intake is one of few modifiable risk factors for cancer, the risk increasing with greater cumulative exposure as a result of longer life expectancy [12]. The current 'low-risk' drinking guidelines of the Australian National Health and Medical Research Council recommend consuming no more than two standard drinks (10 g of alcohol per drink) on any day for both men and women [13]. Recently, the American Society of Clinical Oncology endorsed proactively minimizing excessive exposure to alcohol and determining the role of alcohol use on survival following a diagnosis of cancer [14]. The intake of alcohol is likely to vary across different periods in one's life, and the usual intake over time is thought to correlate more closely than current intake with chronic outcomes such as cancer and mortality [15].

In the present study, using lifetime alcohol intake for participants of a prospective cohort study, we have examined associations of pre-diagnostic alcohol intake with incidence of pancreatic cancer and overall survival following a diagnosis of pancreatic cancer.

Materials and methods

Study population

The Melbourne Collaborative Cohort Study (MCCS) recruited 41,513 Melbourne residents during 1990–1994 [16]. Individuals were recruited through the electoral rolls (registration to vote is compulsory for adults in Australia), advertisements, and community announcements in local media (such as television, radio, newspapers). Participants attended clinics where demographic, anthropometric, lifestyle, and dietary information were collected and anthropometric measurements were performed. Written informed consent was obtained to participate and for investigators to obtain access to medical records. Cancer Council Victoria's Human Research Ethics Committee approved the study protocol. Individuals aged < 40 ($n = 194$) or ≥ 70 years ($n = 131$) at baseline, with a confirmed cancer diagnosis at enrolment ($n = 1{,}511$), with missing or implausibly high alcohol intake ($n = 385$), reporting extreme values of total energy intake ($<$ 1st and $>$ 99th percentile) ($n = 783$), or missing information on other covariates ($n = 37$) were excluded, leaving 38,472 people available for this analysis (Fig. 1).

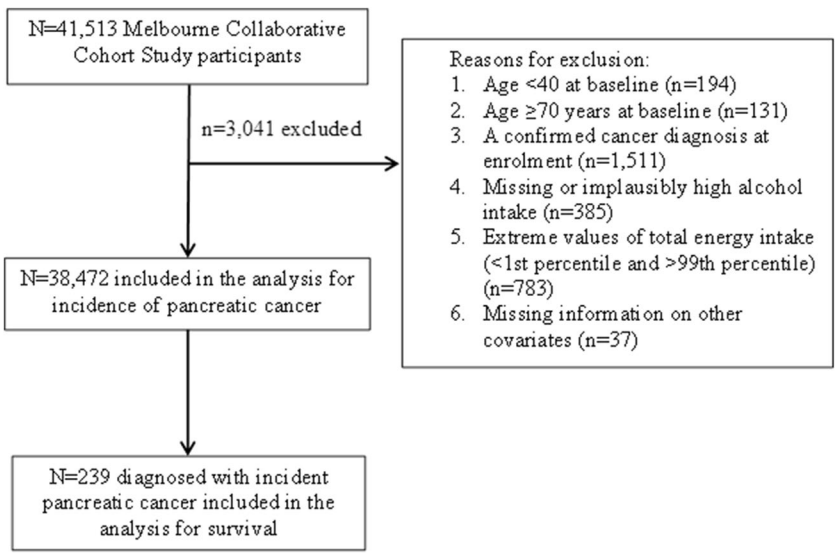

Fig. 1 Flow diagram showing selection of participants

Baseline data collection

A structured interview schedule was used at baseline to obtain information on potential risk factors including sex, country of birth, education, alcohol intake, cigarette smoking, physical activity, energy intake from food, and diabetes mellitus. Physical activity was assessed by three separate questions regarding the frequency of non-occupational vigorous and moderate physical activity, and walking [17, 18] as described by Haydon et al. [19]. The responses to each question were coded as 0 ('none'), 1.5 (1–2 per week), and 4 (≥ 3 per week), and scores for walking and moderate exercise were added together along with two times the score for vigorous exercise to generate a physical activity score for each participant, reflecting the relative energy expenditure of different activity types [20]. This score was grouped based on approximate quartiles for the MCCS. Height was measured to 1 mm with a stadiometer, and weight was measured to 100 g using digital electronic scales [21]. A 121-item food frequency questionnaire (FFQ) was used to collect dietary information [22], including, questions on intake of meat, poultry and fish, dairy and eggs, vegetables, fruit, cereal products, and a section on non-alcoholic beverages and snacks. Intake of nutrients was computed using mean sex-specific portion sizes from weighed food records [22] and Australian food composition tables [23]. Energy intake was estimated from food frequency data, not including energy from alcoholic beverages. This questionnaire was assessed for reproducibility and validity relative to fatty acid and carotenoid biomarkers, and was found to perform similarly to other FFQs [24, 25]. Energy intake was estimated from food frequency data, not including energy from alcoholic beverages.

Assessment of alcohol consumption

Participants were asked if they had ever drunk at least 12 alcoholic drinks in a year. Those who had were then asked about their usual frequency of consumption and usual quantity consumed per drinking occasion for beer, wine, and spirits separately during 10-year age periods commencing at age 20, up to the age decade at baseline attendance. Usual intake within each age period in grams per day for each beverage type was calculated by multiplying intake frequency by quantity and standard amount of alcohol per container using Australian food composition tables [23]. The alcohol intake for each age period in grams per day was calculated as the sum of intake from the three beverage types. Beverage-specific total intakes within age periods were summed to obtain total lifetime intakes in grams. The average lifetime alcohol intake in grams per day was derived by dividing the total lifetime intake by the total number of days within the age intervals up to baseline attendance [26]. Usual lifetime alcohol intake was categorized as follows: lifetime abstainers (reference category: participants who did not report any consumption of alcoholic beverages at each age decade during their lifetime), > 0–19, 20–39, and ≥ 40 g/day. Intake in grams per day for the age period encompassing study enrolment was used as baseline alcohol intake (e.g., for a woman who was 54 years old at enrolment, intake frequency, and quantity reported for age 50–59 were used to calculate her baseline intake).

Cohort follow-up and ascertainment of cases and deaths

Cases and vital status were ascertained through the Victorian Cancer Registry, the Victorian Registry of Births, Deaths and Marriages, the National Death Index and the Australian Cancer Database. The main outcomes were (a) incident cases of pancreatic cancer with histopathological confirmation and coded following the 3rd Revision of the International Classification of Diseases for Oncology (C25 but excluding cancers of the endocrine pancreas (C25.4) which were censored at diagnosis) and (b) overall survival following a diagnosis of incident pancreatic cancer, during follow-up to 30 September 2015.

Statistical analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) [27] for a 10-g/day increment in lifetime, baseline (controlled for former drinkers), and age 20–29 alcohol intake and for intake categories. For pancreatic cancer incidence, age was chosen as the time axis, and follow-up began at baseline and ended at diagnosis of first pancreatic cancer, diagnosis of first other cancer, death, date of leaving Victoria, or 30 September 2015, whichever came first. We considered existing evidence and a causal diagram (directed acyclic graph) to determine confounding variables to be included in the multivariable-adjusted models. The following confounding variables were included in the multivariable-adjusted models: sex, country of birth (Australia, United Kingdom, Greece, Italy), education (primary school, some high/technical school, completed high/technical school, completed tertiary degree/diploma), cigarette smoking (never, former, current smokers), physical activity (score 0, > 0–3.9, ≥ 4–5.9, ≥ 6), body mass index (continuous: per 5 kg/m^2), energy from food not including alcoholic beverages (continuous), and diabetes mellitus (no, yes). Adjusting for parity, oral contraceptive use, and hormone replacement therapy for women did not change the HRs for alcohol intake appreciably and so results from this analysis are not reported.

For survival following pancreatic cancer, time since pancreatic cancer diagnosis was chosen as the time axis, and

analysis time began at date of diagnosis and ended at death or 30 September 2015, whichever came first. The models examining survival were additionally adjusted for the age at diagnosis of pancreatic cancer (continuous).

Dose–response relationships were examined by comparing models that included alcohol intake (continuous) as a linear term only and as restricted cubic splines (3 knots) [28]. Nested models were compared using the likelihood ratio test [29]. A sensitivity analysis was performed excluding the first 2 years of follow-up for incidence analyses. Tests based on Schoenfeld residuals and graphical methods showed no evidence that proportional hazard assumptions were violated. Statistical analyses were performed using Stata 14.1 (StataCorp, College Station, TX). All p values are two-sided, and $p < 0.05$ was considered as statistically significant.

Results

Of all study participants, 50.7% consumed less than two standard drinks of alcohol per day (1 standard drink = 10 g) and 28.8% were lifetime abstainers (Table 1). The median lifetime alcohol intake among non-abstainers was 10.7 g/day. By the end of follow-up (average 20.2 years), 239 incident cases of pancreatic cancer were diagnosed. Most of them were either located in the head of the pancreas (C250) or were unspecified for anatomic site (C259) (Supplementary Table 1). The mean age at which individuals were diagnosed with pancreatic cancer was 73.7 years. Of those diagnosed with pancreatic cancer, 228 individuals had died during 259.9 person-years since diagnosis.

Alcohol intake and pancreatic cancer incidence

A higher lifetime alcohol intake was not associated with incidence of pancreatic cancer (HR 1.01 per 10 g/day increment, 95% CI 0.93–1.09; p value = 0.85) (Table 2). A cubic spline model (with 3 knots placed at 2, 5, and 10 g/day) did not fit appreciably better than a model with a single linear term for lifetime alcohol intake (p value = 0.7); adding more knots did not change the result. Similar findings were observed for baseline and age 20–29 alcohol intakes (Table 2). Excluding the first 2 years of follow-up in sensitivity analyses did not change the HRs appreciably (data not shown).

Alcohol intake and survival following pancreatic cancer

There was evidence of lower overall survival following a diagnosis of pancreatic cancer associated with increasing lifetime alcohol intake [mortality HR 1.09 per 10 g/day increment, 95% CI 1.00–1.19; p value = 0.04 (Table 2); and log-rank test p value = 0.03 (Fig. 2)]. A similar finding was observed with age 20–29 intake [HR 1.09 per 10 g/day increment, 95% CI 1.02–1.18; p value = 0.01 and HR 2.56, 95% CI 1.40–4.68 for an intake of ≥ 40 g/day compared with abstention (Table 2)]. The HR for baseline alcohol intake was 0.95 per 10 g/day increment (95% CI 0.87–1.04; p value = 0.29) (Table 2).

Discussion

While we did not observe an association between alcohol intake and risk of pancreatic cancer, higher pre-diagnostic lifetime and age 20–29 alcohol intakes were associated with lower overall survival following a diagnosis of pancreatic cancer.

One of the main strengths of the present study is the availability of alcohol consumption data from age 20. The overwhelming majority of cohort studies that evaluated the role of alcohol intake in relation to pancreatic cancer risk or survival following diagnosis only captured alcohol intake closer to study enrolment, in contrast to the present study where lifetime intake was used. Other strengths include the prospective nature of the study, near complete follow-up of participants through the population cancer registry, and the low rates of attrition. This study also contributes to a sparse literature by examining the relationship between alcohol intake and survival following a diagnosis of pancreatic cancer. Nevertheless, several limitations exist, and they include the measurement error due to respondents having to summarize their frequency and quantity of alcoholic beverage intake for 10-year age intervals into 'usual' values; the possibility that lifestyle habits and body size could have changed during the period from exposure ascertainment to pancreatic cancer diagnosis, and thereafter due to ill health; potential for present intake to influence recall of past intake and under-reporting of past intake; misclassification of alcohol intake; confounding due to unmeasured factors; and inability to examine pancreatitis as an effect modifier in the association between alcohol intake and pancreatic cancer [30] as that information was not available. Alcohol use is a leading cause of chronic pancreatitis [31], with risk proportional to the dose and duration of alcohol use (minimum, 6–12 years of approximately 80 g of alcohol per day [32]), and chronic pancreatitis in turn is an established risk factor for pancreatic cancer [33]. Also, because details of stage and treatment were not available, we were unable to assess whether they mediated or modified the association between alcohol consumption before diagnosis and survival. Cautious interpretation of findings is also warranted when analyses involve relatively small number of cases of pancreatic cancer or deaths.

Table 1 Characteristics of participants and pancreatic cancer cases in the Melbourne Collaborative Cohort Study

	All participants ($n=38,472$)	Pancreatic cancer cases ($n=239$)
Age at baseline, mean (SD), years	55.2 (8.6)	59.8 (7.5)
Sex, *n* (%)		
Male	15,707 (40.8)	107 (44.8)
Female	22,765 (59.2)	132 (55.2)
Country of birth, *n* (%)		
Australia/New Zealand	26,432 (68.7)	152 (63.6)
United Kingdom	2,850 (7.4)	15 (6.3)
Italy	5,033 (13.1)	40 (16.7)
Greece	4,157 (10.8)	32 (13.4)
Education, *n* (%)		
Primary school	7,397 (19.2)	58 (24.3)
Some high/technical school	14,626 (38.0)	95 (39.7)
Completed high/technical school	7,954 (20.7)	48 (20.1)
Completed tertiary degree/diploma	8,495 (22.1)	38 (15.9)
Lifetime alcohol intake among drinkers, mean (SD), g/day	16.7 (18.5)	17.2 (21.0)
Lifetime alcohol intake categories (g/day)		
Abstention	11,086 (28.8)	67 (28.0)
> 0–19	19,504 (50.7)	123 (51.5)
20–39	5,080 (13.2)	27 (11.3)
≥ 40	2,802 (7.3)	22 (9.2)
Baseline alcohol intake categories (g/day)		
Abstention	11,086 (28.8)	67 (28.0)
Former drinkers	4,043 (10.5)	32 (13.4)
> 0–19	16,067 (41.8)	96 (40.2)
20–39	4,567 (11.9)	24 (10.0)
≥ 40	2,709 (7.0)	20 (8.4)
Age 20–29 alcohol intake categories (g/day)[a]		
Abstention	16,441 (42.7)	110 (46.0)
>0–19	16,009 (41.6)	96 (40.2)
20–39	3,494 (9.1)	16 (6.7)
≥ 40	2,527 (6.6)	17 (7.1)
Cigarette smoking, *n* (%)		
Never	22,289 (57.9)	121 (50.6)
Former	11,931 (31.0)	80 (33.5)
Current	4,252 (11.1)	38 (15.9)
Physical activity, score		
0	8,507 (22.1)	58 (24.3)
> 0–3.9	7,768 (20.2)	44 (18.4)
≥ 4–5.9	13,590 (35.3)	94 (39.3)
≥ 6	8,607 (22.4)	43 (18.0)
Body mass index, mean (SD), kg/m^2	26.9 (4.4)	27.7 (4.7)
Diabetes mellitus, *n* (%)		
No	37,076 (96.4)	225 (94.1)
Yes	1,396 (3.6)	14 (5.9)
Energy intake from food, mean (SD), kJ/day	8,778 (3044)	8,671 (3325)

SD standard deviation

[a]1 participant has missing age 20–29 alcohol intake

Table 2 Hazard ratios (HRs) and 95% confidence intervals (CIs) for pancreatic cancer incidence and survival in relation to alcohol intake

	Participants (*n*)	Cases/ deaths (*n*)	Multivariable-adjusted HR (95% CI)	*p* value*
Incidence[a]				
Lifetime alcohol intake				
For a 10 g/day increment in intake	38,472	239	1.01 (0.93–1.09)	0.85
Intake categories (g/day)				
Abstention	11,086	67	Reference	
> 0–19	19,504	123	1.23 (0.90–1.69)	
20–39	5,080	27	0.96 (0.59–1.57)	
≥ 40	2,802	22	1.30 (0.76–2.23)	
Baseline alcohol intake				
For a 10 g/day increment in intake	38,472	239	0.98 (0.90–1.06)	0.55
Intake categories (g/day)				
Abstention	11,086	67	Reference	
Former drinkers	4,043	32	1.46 (0.94–2.27)	
> 0–19	16,067	96	1.18 (0.85–1.65)	
20–39	4,567	24	0.94 (0.57–1.55)	
≥ 40	2,709	20	1.21 (0.70–2.08)	
Age 20–29 alcohol intake				
For a 10 g/day increment in intake	38,471	239	1.01 (0.94–1.09)	0.79
Intake categories (g/day)				
Abstention	16,441	110	Reference	
> 0–19	16,009	96	1.10 (0.82–1.49)	
20–39	3,494	16	0.77 (0.44–1.36)	
≥ 40	2,527	17	1.02 (0.58–1.78)	
Overall survival[b]				
Lifetime alcohol intake				
For a 10-g/day increment in intake	239	228	1.09 (1.00–1.19)	0.04
Intake categories (g/day)				
Abstention	67	65	Reference	
> 0–19	123	116	0.76 (0.54–1.07)	
20–39	27	27	0.82 (0.48–1.39)	
≥ 40	22	20	1.60 (0.90–2.83)	
Baseline alcohol intake				
For a 10 g/day increment in intake	239	228	0.95 (0.87–1.04)	0.29
Intake categories (g/day)				
Abstention	67	65	Reference	
Former drinkers	32	32	0.86 (0.54–1.37)	
> 0–19	96	89	0.80 (0.56–1.15)	
20–39	24	24	1.13 (0.65–1.97)	
≥ 40	20	18	0.62 (0.35–1.12)	
Age 20–29 alcohol intake				
For a 10-g/day increment in intake	239	228	1.09 (1.02–1.18)	0.01
Intake categories (g/day)				
Abstention	110	106	Reference	
> 0–19	96	91	1.07 (0.79–1.45)	
20–39	16	15	1.12 (0.57–2.22)	
≥ 40	17	16	2.56 (1.40–4.68)	

*p values (two-sided) were determined using Wald test from Cox regression models assessing linear trends for a 10 g/day increment in intake

[a]Adjusted for sex, country of birth (Australia, United Kingdom, Greece, Italy), education (primary school, some high/technical school, completed high/technical school, completed tertiary degree/diploma), cigarette

Table 2 (continued)

smoking (never, former, current smokers), physical activity (score 0, > 0–3.9, ≥ 4–5.9, ≥6), body mass index (continuous: per 5 kg/m^2), energy from food not including alcoholic beverages (continuous), and diabetes (no, yes); baseline alcohol intake (continuous) additionally adjusted for former drinking (yes, no)

[b]Adjusted for age at diagnosis of pancreatic cancer (continuous), sex, country of birth (Australia, United Kingdom, Greece, Italy), education (primary school, some high/technical school, completed high/technical school, completed tertiary degree/diploma), cigarette smoking (never, former, current smokers), physical activity (score 0, >0–3.9, ≥4–5.9, ≥6), body mass index (continuous: per 5 kg/m^2), energy from food not including alcoholic beverages (continuous), and diabetes (no, yes); baseline alcohol intake (continuous) additionally adjusted for former drinking (yes, no)

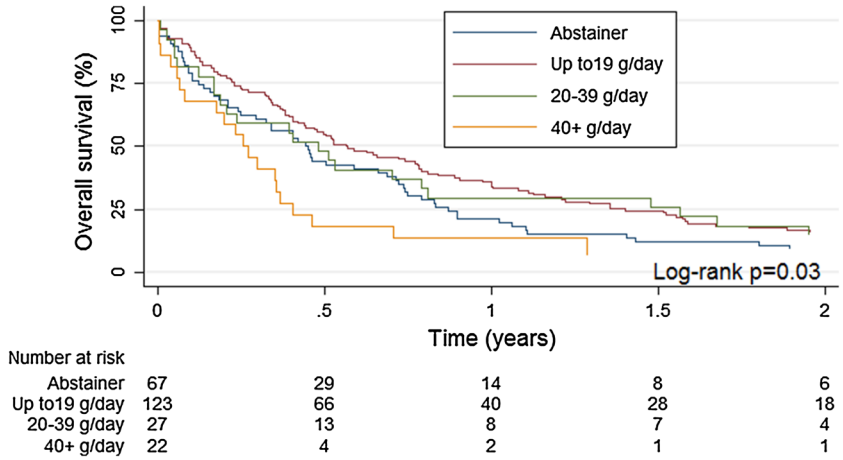

Fig. 2 Kaplan–Meier curves for overall survival following a diagnosis of pancreatic cancer by lifetime alcohol intake

Evidence for the role of alcohol use in pancreatic cancer incidence from cohort studies is equivocal. The most recently published results, to our knowledge, from the European Prospective Investigation into Cancer and Nutrition (EPIC) (1,283 incident pancreatic cancers diagnosed from 476,106 participants) reported HRs of 1.77 (95% CI 1.06–2.95) and 1.63 (95% CI 1.16–2.29) for lifetime and baseline alcohol intake, respectively, comparing intake over 60 g/day to the reference category 0.1–4.9 g/day [34]. The similarly large US National Institutes of Health-AARP Diet and Health Study (1,149 pancreatic cancer cases from 470,681 participants) had previously found a similar association for an alcohol intake of ≥3 drinks/day compared with <1 drink/day [35]. The Netherlands Cohort Study, which included 350 cases from 120,852 participants, reported a HR of 1.57 (95% CI 1.03–2.39) for all cases and a HR of 1.54 (95% CI 0.94–2.54) for microscopically confirmed cases, comparing an intake of ≥30 g/day with abstention [36]. None of these three studies found associations for women; at least partially attributable to their relatively low levels of drinking compared with men. Meta-analyses to date have only found an increased risk of pancreatic cancer with intakes of 3 or more drinks per day [30, 37–39]. In the present study, almost 80% of the participants either consumed only ≤2 drinks/day or were lifetime abstainers limiting the evaluation of drinking as a risk factor for pancreatic cancer in our cohort. It is believed that alcohol and its metabolites could alter metabolic pathways involved in the inflammatory response and carcinogenesis, dysregulate proliferation and apoptosis, and cause other genetic and epigenetic effects, leading to pancreatic cancer [40]. It can also lead to premature intracellular activation of digestive enzymes and autodigestive injury to the pancreas [41]. Alcohol use is also known to augment the carcinogenic effects of cigarette smoking [42].

Most studies that have assessed survival following a diagnosis of pancreatic cancer according to alcohol use have collected alcohol intake data for the period around study enrolment and have reported inconsistent findings [43–47]. One study that reported results consistent with our findings was the Cancer Prevention Study II where an association between an alcohol intake of ≥3 drinks/day and lower survival following pancreatic cancer was observed using over a million participants from which nearly 7,000 pancreatic cancer deaths were identified [47]. That study used information on current alcohol intake at study enrolment, and if intake had changed in the preceding 10 years, participants were asked to report their previous intake; participants who reported past but no current alcohol intake were excluded from the analysis [47]. Thus far, early detection of pancreatic cancer through surveillance has remained elusive with no known tumor marker or high-risk subgroup that could benefit from screening. Detection of pre-neoplastic lesions and identification of predisposing diseases like papillary mucinous tumors of the pancreas, chronic pancreatitis, or hereditary cancer syndromes will also not alter prognosis

overall since they account for only a fraction of the pancreatic cancers [2]. Modifying high-risk behavior including limiting alcohol intake might afford a unique opportunity for enhancing survival but more epidemiologic research is needed to confirm potential biological pathways involved and molecular/anatomical subtypes of pancreatic cancer affected, and how these might interact with treatment. It was not possible to assess the associations for survival by anatomic site in the pancreas (head; body; tail; duct; other) in the present study due to the small number of cases in sites other than the head of the pancreas. For example, pancreatic ductal adenocarcinoma is widely recognized as one of the 'incurable cancers' due to its aggressive clinical course [48], but the number of ductal adenocarcinomas was not adequate for a meaningful comparison.

In conclusion, while we cannot confirm a role for alcohol use in the etiology of pancreatic cancer, our finding for enhanced survival following lower alcohol intake from an early age needs to be confirmed by other similar studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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