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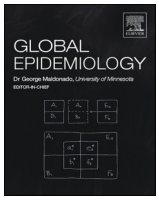

# Alcohol consumption and incidence of pancreatic cancer

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ABSTRACT

*Purpose:* The association between alcohol consumption and pancreatic cancer is unsettled.
*Methods:* Altogether 243,169 men and women 20–79 years, without cancer at baseline, were followed with respect to pancreatic cancer by linkage to the Cancer Registry of Norway and the Norwegian Cause of Death Registry. They participated in a cardiovascular survey where information on alcohol consumption, smoking habits, anthropometric measures, and some biological variables were recorded. During 20 years of follow-up, 991 incident pancreatic cancers were registered. We estimated the hazard ratios with the Cox proportional hazards model, and graphed spline curves between glass-units/d of alcohol and hazard ratio of incident pancreatic cancer.
*Results:* The multivariable adjusted hazard per 1 glass-unit/d was 1.08 (95% confidence interval 1.02–1.15) for men and 1.04 (0.97–1.13) for women. The association between alcohol consumption and incident pancreatic cancer was present in ex- and current smokers, but the association could be ascribed to smoking habits. The multivariable adjusted spline curves increased with increasing glass-units/d and with confidence bands not encompassing 1.0 above one glass-unit/day.
*Conclusion:* Our findings of an association between higher level of alcohol consumption and incident pancreatic cancer, could be attributed to confounding by smoking habits.

## Introduction

Pancreatic cancer is the seventh leading cause of cancer-related deaths worldwide, but the second most frequent gastrointestinal cancer in the Western world. Incidence and mortality vary considerably with higher figures in the developed countries [1]. The incidence and mortality rates of pancreas cancer in Norway were around 6–8 per 100,000 per year from 1965 to 2007, but survival after diagnosis of pancreatic cancer remains very low with 1-year survival rates of 18% and 16% for males and females, respectively, making pancreatic cancer the fourth leading cause of death by cancer in that country [2]. Potential risk factors are tobacco smoking, dietary factors, alcohol abuse, diabetes mellitus, obesity, age, ethnicity, family history, and genetic factors, but direct causal associations remain mainly unknown [3]. Identifying the etiological factors is the only means to prevent this fatal disorder. The association between a Healthy Lifestyle Index (HLI) and pancreas cancer was examined within the European Prospective Investigation into Cancer and Nutrition cohort, or EPIC study [4]. They were able to demonstrate a protective effect of healthy lifestyle, partly depending on obesity distribution and the inclusion/exclusion of smoking. Alcohol consumption was included in the index, but the exclusion of alcohol did not affect the associations with the lifestyle score and cancer of the pancreas. Thus, the association between alcohol consumption and pancreatic cancer remains unsettled. We had access to a large follow-up study on men and women in Norway that was linked to the Cancer Registry of Norway and the Norwegian Cause of Death Registry. This enabled us to analyze self-reported alcohol consumption as a risk factor for pancreatic cancer, taking smoking and other potential risk factors into consideration.

## Methods

The data stems from 276,581 men and women aged 20–79 years who participated in cardiovascular surveys in 1994–2002, and of whom 6928 were registered in the Norwegian Cancer Registry [5,6]. The participation rate was between 65% and 75%, and 26,464 had missing variables

*Abbreviations:* BMI, Body Mass Index; HDL-C, High density lipoprotein cholesterol; CI, Confidence interval; Ref, Reference category; Pyrs, Person years.

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in one or more of the covariates mentioned beneath, leaving 243,169 as our study population.

*Exposure variables*

The participants received a questionnaire that was to be filled in at home and taken to the screening site where it was checked for inconsistencies by trained nurses [5,6]. At the screening site weight (kg), height (cm), and blood pressure were measured. A non-fasting blood sample was drawn, and serum analyzed for total cholesterol, triglycerides, and HDL cholesterol.

*Alcohol consumption*

Two non-overlapping questions on alcohol consumption were used: 1) "How many glasses of beer, wine, or spirits do you usually drink during a 14-days period?". We added the number of glasses for each alcohol type and divided it by 14 to get glass-units/day. 2) "How often do you drink alcohol during a year", with preset alternatives: 4–7 times/week, 2–3 times/week, once/week, 2–3 times/month, once/monthly, a few times last year, no alcohol last year, never used alcohol. "When you drink alcohol, how many glasses do you usually drink?". The frequency alternatives were reclassified to 5.5 times/week, 2.5 times/week, 1 time/week, 0.625 times/week, 0.25 times/week, and 0.077 times/week (a few times last year set to 4 times last year), and zero. Multiplication with the number of glasses each time and division by 7 gave glass-units/day.

*Covariates*

We asked about smoking habits classified as never, ex and current smokers. For current smokers we asked about number of cigarettes smoked per day, where the participants filled in the actual number between 0 and 99. We defined 5 smoking categories: Never, Ex, 0–9, 10–19, ≥20 cigarettes/day. This variable was entered as a factor variable in the multivariable analyses, with Never as the reference category. Two non-overlapping questions on physical activity were used. One about physical exertion during leisure time that concerned the last year period, with the following alternatives: Sedentary, moderate, intermediate, hard. The second question was about hard physical activity during leisure time during the last year with the alternatives no activity, < 1, 1–2, 3 or more hours per week. We categorized the participants with moderate or more, or at least 1 h of hard activity per week as physically active. Marital status was classified as unmarried (yes, no). The length of formal education was collected from Statistics Norway with 8 categories: 1 ≤ 7 years, 2 = 7–9, 3 = 10. 4 = 11–12, 5 = 13–14, 6 = 15–16, 7 = 17–18, 8 ≥ 18 years. The question about diabetes read: "Have you, or have you had diabetes (yes, no)?"

*Endpoints*

The participants accrued person-years from date of participation until the date of death, date of cancer, or December 31, 2018, whichever came first. The cancer diagnosis was retrieved from linkage with the Cancer Registry of Norway and the Norwegian Cause of Death Registry.

*Statistics*

We used the margins procedure in STATA to adjust mean values for age. The margins procedure estimates margins of responses at specified values of the covariate (age). We used linear regression and specified mean values. Equality across the glass-units/d groups was tested by the likelihood ratio test in model with and without the three glass-units/d groups [7]. We used the direct method, with internal standard population in ten-years age group, to estimate age-adjusted incidence rate. We estimated hazard ratios with Cox proportional hazards models with incident pancreatic cancer as the outcome, one run with age as a covariate in addition to glass-units/day and one with age and the variables described above as covariates. We assessed interaction by the likelihood ratio test from models with and without the interaction terms. Linearity was tested from Cox models with and without a second order term of glass-units/day. We graphed spline curves using the mkspline package with restricted cubic spline construction (4 knots) combined with the xblc package in STATA [7]. The proportional hazards assumption was tested based on the Schoenfeld residuals [7].

## Results

*19% of men and 33% of women were non-drinkers*

The share of current smokers increased, while the share of never smokers decreased with consumption of alcohol (measured in glass-units/day) (Table 1). HDL-cholesterol, and the share of unmarried individuals increased with consumption of alcohol. Alcohol consumption was also positively associated with educational level and body height levelling off at ≥2 glass-units/day.

The total number of person-years was 4,618,723, and 991 cases with pancreatic cancer, 541 men and 450 women, were recorded during the follow-up period. The average follow-up was 20 years.

The age-adjusted incidence of pancreas cancer was 25 per 100,000 pyrs (95% CI: 22–27) in men and 20 per 100,000 pyrs (95% CI: 18–22) in women.

We found no evidence that the proportional hazards assumption for glass-units/day was violated, and it was no evidence of departure from linearity of the association glass-units/day and incidence of pancreatic cancer.

**Table 1**
Baseline characteristics by alcohol consumption. Men and women 20–79 years.

| | Alcohol, glass-units/day | | | |
|---|---|---|---|---|
| | MEN | | | |
| | 0 | >0 – <1 | 1 – <2 | ≥2 |
| N | 22,350 | 80,660 | 12,363 | 2514 |
| Age (mean) | 48 | 46 | 44 | 46 |
| Age-adjusted values | | | | |
| Never smoker (%) | 48 | 44 | 46 | 39 |
| Ex smoker (%) | 39 | 39 | 33 | 32 |
| Current smoker (%) | 14 | 17 | 21 | 29 |
| Education (1 = low, 2, 3...., 8 = high) | 3.8 | 4.2 | 4.4 | 4.4 |
| Height (cm) | 177.6 | 178.5 | 178.9 | 178.7 |
| BMI (kg/m$^2$) | 26.4 | 26.3 | 26.4 | 26.3 |
| Cholesterol (mmol/l) | 5.8 | 5.8 | 5.8 | 5.9 |
| Triglycerides (mmol/l) | 2.1 | 2.0 | 2.0 | 2.1 |
| HDL-C (mmol/l) | 1.2 | 1.2 | 1.3 | 1.4 |
| Systolic blood pressure (mmHg) | 135 | 134 | 135 | 137 |
| Unmarried (%) | 24 | 22 | 27 | 35 |
| Diabetes (%) | 3.0 | 1.9 | 1.6 | 2.2 |
| | WOMEN | | | |
| N | 42,039 | 79,339 | 3517 | 387 |
| Age (mean) | 47 | 43 | 44 | 46 |
| Age-adjusted values | | | | |
| Never smoker (%) | 50 | 46 | 44 | 33 |
| Ex smoker (%) | 36 | 35 | 29 | 25 |
| Current smoker (%) | 14 | 19 | 27 | 42 |
| Education (1 = low, 2, 3...., 8 = high) | 3.7 | 4.1 | 4.6 | 4.4 |
| Height (cm) | 164.5 | 165.6 | 166.6 | 166.2 |
| BMI (kg/m$^2$) | 25.9 | 25.0 | 24.4 | 24.5 |
| Cholesterol (mmol/l) | 5.7 | 5.5 | 5.5 | 5.5 |
| Triglycerides (mmol/l) | 1.5 | 1.4 | 1.3 | 1.3 |
| HDL-C (mmol/l) | 1.4 | 1.5 | 1.6 | 1.7 |
| Systolic blood pressure (mmHg) | 128 | 126 | 125 | 126 |
| Unmarried (%) | 17 | 17 | 21 | 30 |
| Diabetes (%) | 2.3 | 1.2 | 0.6 | 0.7 |

The risk of pancreas cancer in men was higher in the 2+ glass-units /day group than in the below 1 glass-units/day group (Table 2). In women only 1-one case gave a very unprecise estimate. The risk increase per 1 glass-unit/day was 8% in men and 4% in women after multivariable adjustment.

There was no factorial interaction for sex-glasses/day with all variables in the model.

Table 3 shows the hazard ratios for men and women combined, by glass-units/day and smoking groups. The hazard ratio for pancreatic cancer did not increase with increasing alcohol consumption in never smokers. The hazard ratios for current smokers were higher than for non-smokers and showed an increasing trend with higher alcohol consumption. However, this trend was not present when number of cigarettes was taken into consideration. The increased hazard ratio with high alcohol consumption in ex-smokers was not significant. There was no factorial interaction smoking categories – number of glasses.

The stratified analyses showed a stronger association between alcohol consumption and pancreatic cancer in older people, people with longer education, people with higher body mass index, and people with diabetes (Table 4). However, wide confidence intervals suggest that these stronger associations might be ascribed to chance.

There was increasing risk of pancreatic cancer with increasing glasses/day with the lower confidence bands above 1.0 for alcohol intake above 1 glass-unit/d (Fig. 1).

## Discussion

We found an increased risk of pancreatic cancer with increasing alcohol consumption, most distinct above 1 alcohol glass/day. The association could be explained by smoking habits.

Our findings are in line with studies reporting an association between high alcohol intake and pancreatic cancer, where 30 g/day has been used as a cut-off [8,9]. This corresponds roughly to 2.5 glasses/day.

Responses to questionnaires on alcohol consumption are often regarded as inaccurate, potentially biased and with questionable validity. A major problem is that alcohol consumption and habits vary during a lifetime, and the questionnaire gives only a glimpse of this consumption. Another issue is the potential bias induced by underreporting. This is most likely to occur in the higher consumption categories resulting in underestimating the risk with increased intake.

The choice of reference population is also a matter of concern. The category of non-drinkers consists of never-drinkers and previous drinkers. The latter may have stopped drinking due to health problems.

**Table 2**
Hazard ratios (HR) for pancreatic cancer with 95% confidence intervals. Men and women 20–79 years.

| Glass-units/day | MEN | | | | |
|---|---|---|---|---|---|
| | N cases | HR[a] | 95% CI | HR[b] | 95% CI |
| 0 | 113 | 0.93 | 0.66–1.30 | 0.92 | 0.65–1.30 |
| >0 – <1 | 360 | Ref | | Ref | |
| 1 – <2 | 49 | 0.99 | 0.74–1.34 | 0.99 | 0.73–1.34 |
| ≥2 | 19 | 1.82 | 1.07–3.09 | 1.73 | 1.01–2.94 |
| Per 1 glass-unit/d | 541 | 1.09 | 1.02–1.15 | 1.08 | 1.02–1.15 |
| | WOMEN | | | | |
| 0 | 179 | 0.73 | 0.42–1.29 | 0.70 | 0.39–1.25 |
| >0 – <1 | 257 | Ref | | Ref | |
| 1 – <2 | 13 | 0.84 | 0.48–1.47 | 0.83 | 0.47–1.45 |
| ≥2 | 1 | 0.67 | 0.09–5.10 | 0.61 | 0.08–4.71 |
| Per 1 glass-unit/d | 450 | 1.05 | 0.97–1.14 | 1.04 | 0.97–1.13 |

[a] Adjusted for age.
[b] Adjusted for age, smoking categories, body mass index, height, total cholesterol, triglycerides, HDL cholesterol, systolic blood pressure, educational length, physical activity, unmarried status, and history of diabetes.

**Table 3**
Hazard ratios (HR) for pancreatic cancer with 95% confidence intervals (95% CI) by number of cigarettes and number of alcohol glasses per day. Men and women 20–79 years.

| Smoking groups | Glass-units/day | N cases | HR[a] | 95% CI | HR[b] | 95% CI |
|---|---|---|---|---|---|---|
| Never | 0 | 92 | 0.96 | 0.75–1.24 | 0.92 | 0.72–1.20 |
| Never | >0 – <1 | 189 | Ref | | Ref | |
| Never | ≥1 | 21 | 0.92 | 0.59–1.45 | 0.94 | 0.60–1.48 |
| Ex | 0 | 136 | 0.78 | 0.61–0.99 | 0.75 | 0.58–0.96 |
| Ex | >0 – <1 | 264 | 0.89 | 0.73–1.10 | 0.91 | 0.74–1.12 |
| Ex | ≥1 | 35 | 1.13 | 0.78–1.64 | 1.23 | 0.84–1.79 |
| Current | 0 | 64 | 1.49 | 1.11–2.01 | 1.43 | 1.07–1.94 |
| Current | >0 – <1 | 164 | 1.53 | 1.23–1.90 | 1.53 | 1.23–1.91 |
| Current | ≥1 | 26 | 1.72 | 1.13–2.60 | 1.82 | 1.20–2.75 |

[a] Adjusted for sex and age.
[b] Adjusted for sex, age, body mass index, height, total cholesterol, triglycerides, HDL cholesterol, systolic blood pressure, educational length, physical activity, unmarried status, and history of diabetes.

**Table 4**
Hazard ratios (HR) with 95% confidence intervals (95% CI) for pancreatic cancer stratified by age, educational length, BMI, and history of diabetes.

| | Glass-units/d | n deaths | HR[a] (95% CI) |
|---|---|---|---|
| Age[b] | | | |
| <50 years | <1 | 369 | Ref |
| <50 years | ≥1 | 33 | 1.00 (0.70–1.44) |
| ≥ 50 years | <1 | 540 | 6.89 (5.74–8.26) |
| ≥ 50 years | ≥1 | 49 | 9.57 (6.91–13.2) |
| Educational length[b] | | | |
| <15 years | <1 | 751 | Ref |
| <15 years | ≥1 | 49 | 1.04 (0.77–1.39) |
| ≥ 15 years | <1 | 158 | 0.84 (0.70–1.00) |
| ≥ 15 years | ≥1 | 33 | 1.26 (0.88–1.79) |
| Body mass index[b] | | | |
| <30 kg/m$^2$ | <1 | 759 | Ref |
| <30 kg/m$^2$ | ≥1 | 69 | 1.16 (0.90–1.49) |
| ≥30 kg/m$^2$ | <1 | 150 | 1.04 (0.87–1.25) |
| ≥30 kg/m$^2$ | ≥1 | 13 | 1.54 (0.89–2.69) |
| Diabetes[b] | | | |
| No | <1 | 874 | Ref |
| No | ≥1 | 79 | 1.18 (0.93–1.50) |
| Yes | <1 | 35 | 1.33 (0.94–1.88) |
| Yes | ≥1 | 3 | 2.15 (0.69–6.71) |

[a] Adjusted for sex, age, smoking categories, body mass index, height, total cholesterol, triglycerides, HDL cholesterol, systolic blood pressure, educational length, physical activity, unmarried status, and history of diabetes.
[b] Not in model when stratified.

It is possible that people have reduced or quit alcohol intake due to diabetes or pancreatitis, and in this material the prevalence of diabetes was highest among non-drinkers.

Smoking and alcohol may share the pathways to pancreatic cancer. The association between alcohol and pancreatic cancer could be attributed to the smoking history. Although these associations could be ascribed to chance, we cannot exclude the possibility of enhanced risk at higher consumption of alcohol than this study could provide.

Data from two other large cohort studies have not supported an association between alcohol consumption and pancreatic cancer [10]. Two mendelian randomization studies gave opposite results. Larsson et al. found no association, whereas a Lu et al. confirmed that alcohol could be a causal factor [11,12]. Larsson et al. emphasize that the main limitation of their study was low precision in some analyses, particularly for analyses of alcohol consumption and site-specific cancer.

Thus, the associations regarding alcohol and pancreatic cancer are contradictory; illustrated also by the following references that are all supporting an association [8,9,13]. The reasons for these discrepant results are not clear, but the studies differ concerning magnitude, length

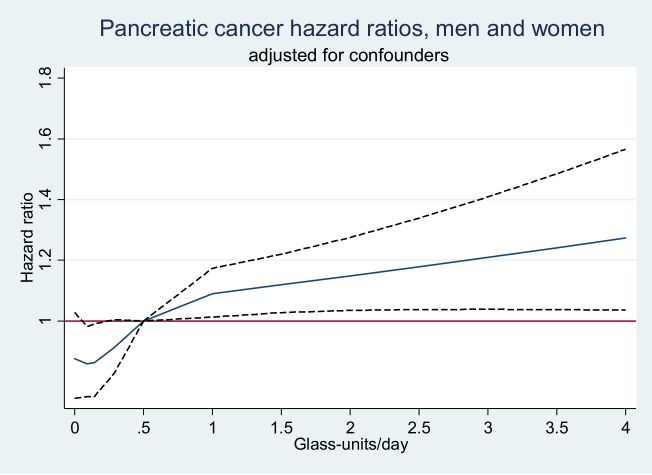


**Fig. 1.** Spline curves with 95% confidence bands on the association between alcohol consumption and incident pancreatic cancer. Adjusted for sex, age, smoking categories, body mass index, height, total cholesterol, triglycerides, HDL cholesterol, systolic blood pressure, educational length, physical activity, unmarried status, and history of diabetes.

of follow-up, and population characteristics. The study from the Netherlands showed for instance an association between alcohol and pancreas cancer for the first seven years of the follow-up, but not thereafter [8].

Smoking is a risk factor for pancreatic cancer, but whether smoking influences the alcohol-pancreatic cancer association remains unsettled [3,14]. Gapstur et al. found that alcohol consumption increased pancreatic cancer mortality in never smokers [15]. Smoking might also interact with body mass index, as there is a weaker association between body mass index and pancreatic cancer among current smokers than among never smokers [16]. Our study shows that smoking modifies the alcohol-pancreatic cancer association.

Moreover, smoking and alcohol consumption have been previously associated with increased visceral fat deposition [17,18]. This may suggest common pathways between smoking, alcohol consumption and central adiposity in pancreas carcinogenesis.

The EPIC study reported an inverse association between a healthy lifestyle and pancreatic cancer [19]. Smoking status, alcohol intake waist-hip ratio, diet and physical activity composed a healthy lifestyle index. The association persisted beyond the smoking status. We lack information on diet in our study.

Body height is positively associated with many cancer sites, but it is unsettled whether pancreatic cancer is one of these. A review and meta-analysis of cohort studies indicated that height is positively associated with pancreatic cancer risk [20]. The Million Women study found a non-significant positive association [21] which persisted only in never smokers. We have accounted for the potential impact of height.

The strength of our study is a large study with a complete follow-up with two quality registries. To our knowledge this is largest single study of alcohol consumption and pancreas cancer measured by the number of cases. However, few participants reported high consumption of alcohol resulting in imprecise estimates in high consumption groups.

One limitation of our study is that we have recorded alcohol consumption only on a single occasion and we have a specification of type of alcohol in only half of the study population. Furthermore, few heavy drinkers in our study gave unprecise estimates of the association between heavy drinking and pancreatic cancer. Finally, a large share of non-drinkers is suboptimal, as there may be many reasons behind non-drinking.

In conclusion, our study supports that the association between alcohol consumption and pancreatic cancer, is heavily modified by smoking habits.

## Ethics approval

The study was approved by the Norwegian Data Protection Authority and the Regional Committees for Medical and Health Research Ethics.

## Data availability

The ethics approval took for granted that the data was available only to persons who have signed a confidentiality obligation.

## Funding information

No funding beyond usual salaries.

## Declaration of Competing Interest

All three authors declare no conflict of interest.

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