Different Markers of Alcohol Consumption, Smoking and Body Mass Index in Relation to Risk of Pancreatic Cancer. A Prospective Cohort Study within the Malmö Preventive Project.

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Published in:
Pancreatology

DOI:
10.1159/000212088

2009

Title:

Different markers of alcohol consumption, smoking and body mass index in relation to risk of pancreatic cancer: a prospective cohort study within The Malmö Preventive Project.

Short title:
Alcohol and pancreatic cancer

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† The author's whish, with appreciation, to acknowledge the contribution made to this paper by Professor Anders Borgström, who passed away on 9 October 2007.

Abbreviations:
BMI: Body Mass Index, RR: Relative Risk, CI: Confidence Interval, Mm-MAST: Malmö modification of the brief MAST, γ-GT: γ-Glutamyl transferase

Key words:
Pancreatic cancer, epidemiology, smoking, alcohol, body mass index, weight gain.

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Abstract

Background/Aim: The association between alcohol consumption and pancreatic cancer is not clear. This study investigates different pre-diagnostic measurements of alcohol consumption, a laboratory marker (γ-glutamyltransferase (γ-GT)), and a score measuring alcohol addiction (Mm-MAST), in relation to the risk of pancreatic cancer. Furthermore it was investigated whether smoking and alcohol consumption interact with each other, or if the risk of pancreatic cancer associated with these factors is modified by obesity or weight gain.

Methods: A cohort of 33,346 subjects provided pre-diagnostic information on the above factors. During a mean follow-up of 22.1 years, 183 cases of pancreatic cancer occurred. Cox's analysis yielded relative risks (RR) with 95% confidence intervals.

Results: The highest γ-GT quartile was associated with a high risk of pancreatic cancer (RR=2.15:1.34-3.44), and this association were even stronger in subjects that reported a previous weight gain (3.61:1.29-10.09). A high Mm-MAST score was also associated with pancreatic cancer ($p = 0.02$). Current smoking was associated with pancreatic cancer (2.34:1.60-3.43), and obese smokers had an even higher risk (7.45:1.65-33.64).

Conclusion: High alcohol intake is associated with subsequent risk of pancreatic cancer and this risk may be higher following weight gain. The risk associated with smoking may be even higher in obese subjects.

Introduction

There is a well-established association between smoking and pancreatic cancer, explaining about 25% of all cases [1]. In addition, a previous pilot study from Malmö has shown that weight gain may modify this relation [2]. The association between alcohol consumption and pancreatic cancer has been less clear and previous studies have reported inconsistent results [3-15]. Some showed a positive association [5-7,11,14,15], most of which were cohort studies [5,7,14,15], whereas others did not show any association [3,4,8-13] and this was mainly case-control studies [3,4,11-13].

A problem in studies on alcohol is that self-reported consumption may have a low validity. It is difficult to establish previous drinking habits and retrospective and cross-sectional studies may be subject to recall bias or changed alcohol consumption due to sub-clinical disease. Another possible reason for inconsistent results in previous studies on alcohol and pancreatic cancer is that the prevalence of potential interacting factors such as smoking and obesity might have differed between studies.

In 1974 The Department of Medicine, Malmö, Sweden, set up a primary preventive project. Until 1992, a total of 33,346 individuals participated in the baseline examination, which included a physical examination measuring weight and height, laboratory analyses and a questionaire that assessed smoking and alcohol consumption [16]. In this cohort, 183 cases of incident pancreatic carcinomas were diagnosed up until 31 Dec. 2004.

The aim of this study was to investigate whether different pre-diagnostic measurements of alcohol consumption, laboratory markers and a score measuring alcohol addiction, are associated with the risk of developing pancreatic cancer. An additional aim was to investigate the potential interaction between smoking and alcohol consumption in relation to the risk of pancreatic cancer, and if their association with pancreatic cancer is modified by body mass index (BMI) or weight gain.

Material and methods

The Malmö Preventive Project

The Malmö Preventive Project was set up in 1974, as an integrated institute within The Department of Medicine at Malmö, University Hospital, Sweden. The main purposes of the Institute were to screen a middle-aged population for risk factors such as cardiovascular diseases and alcoholism and thereby develop methods, on an individual patient basis, for early detection, health education and prevention of a number of diseases and risk factors [16]. Complete birth-year cohorts of registered residents in Malmö, were invited by letter to participate. All men born in 1921, 1926-42, 1944, 1946 and in 1948-49, and all women born in 1926, 1928, 1930-38, 1941 and in 1949 received an invitation. The attendance rate was high (71%), and when the recruitment ended in 1992, a total of 33,346 individuals (22,444 men and 10,902 women) had participated. Mean age at baseline was 50 years for men and 44 years for women. At baseline examinations subjects responded to a self-administered questionnaire, consisting of about 200 questions concerning lifestyle and medical history. Weight and height were measured by a trained nurse. Selected biochemical analyses were performed, and the remaining biological material was stored in a biological specimen bank. Except for about 6000 men, none of the examinations were repeated following baseline examinations.

Ethical clearance for the present study was obtained from the Ethical Committee at Lunds University, LU-828-02.

Registration of endpoints

Information on cancer diagnosis was retrieved by record linkage to the Swedish Cancer Registry and the Regional Tumor Registry of Southern Sweden. All cases of pancreatic cancer were identified using the ICD 7 code 157, and ICD 10 code C25. Cause and date of

death were established using The Swedish Cause-of-Death Registry. End of follow-up was 31 December 2004. The record linkage yielded 187 cases of incident pancreatic cancer among participants in The Malmö Preventive Project. There were no prevalent cases at baseline. The record for all incident cases were reviewed using clinical notes, radiological - and pathological findings, i.e.; biopsies, specimen obtained during surgery and autopsy reports.

After reviewing these cases, 183 subjects could be confirmed to have adenocarcinoma of the pancreas. In 70 cases the diagnosis was verified by autopsy, 19 cases had undergone surgery and had a clear histopathological diagnosis. Another 82 cases had the diagnosis based on tissue biopsy consistent with adenocarcinoma of the pancreas, their clinical presentation and radiological findings. A further 7 cases were verified by the combination of clinical notes, radiological examination and biopsies that showed unspecified adenocarcinoma, findings that taken together stated a high probability for cancer of the pancreas. Finally, 5 cases were accepted by their clinical and radiological findings, although no biopsies had been taken. Four cases were found to have had pancreatic cancer other than adenocarcinoma, according to their histopathology report (two islets cell tumors, one endocrine and one anaplastic malignancy) and were hence excluded. Thus, 183 subjects remained in the present study as incident pancreatic cancers. This group consisted of 128 men (mean age at diagnosis: 64 years) and 55 women (65 years).

Assessment of potential risk factors

Alcohol

Two independent methods were used to estimate alcohol consumption. One method was the use of a biochemical marker, serum γ-glutamyl transferase (γ-GT), and the second method was a scoring system based on a modified version of the Michigan Alcoholism Screening Test [17], referred to in this text as the “Malmö modification of the brief MAST” (Mm-MAST)

[18]. The scoring system consisted of seven questions regarding drinking habits and has been described in detail elsewhere[19]. Every question gave one point for a positive answer, and no points for a negative answer. Alcohol consumption was regarded as "low" for subjects with a scoring of 0-1, "intermediate" with a scoring of 2-3 and "high" for subjects with a scoring of 4 or more. Alcohol consumption was registered as "missing" for subjects with one or more missing answers. Questions on absolute amounts of alcohol intake were not used in the questionnaire.

These questions were not introduced into the questionnaire until December 1976; hence there were no information on Mm-MAST for the first 2,142 subjects. Missing answers for one or more of the questions were found in 753 subjects. The total number of individuals that could be classified according to this scoring system was 30,551.

Serum γ-Glutamyl transferase (γ-GT)

A standard laboratory method, using γ-glutamyl-p-nitroanilin as a substrate, was used by Malmö University Hospital, to analyse plasma-γ-GT [20]. In all but 107 individuals, information on γ-GT levels were available. For further analysis, the cohort was divided into quartiles based on γ-GT at baseline.

Body mass index and weight gain

At baseline all subjects underwent measurement of height (cm) and weight (kg). These measurements were used to calculate body mass index as kg/m². The following definitions were used; underweight was defined as BMI < 20, normal weight as BMI of 20-25, overweight as BMI 25-30 and obesity as BMI > 30.

The question "Have you gained more than 10 kg since the age of 30?", with the possible answers "yes" or "no", were used in order to define weight gain.

Smoking habits

The question "Have you ever been smoking on a daily basis for at least six months?" and "Are you smoking?" were used to define "never" and "ever" smokers. If the answer was negative for both questions, the subject was classified as "never smokers". Ever smokers that confirmed smoking on a daily basis were regarded as current smokers. Ever smokers that denied daily smoking were considered former smokers. Missing and inconsistent answers could be identified and completed, using other questions concerning smoking habits (daily tobacco dose and time since cessation). These questions were further used to define the amount of daily smoking in current smokers and time since smoking cessation in former smokers. The questionnaire consisted of questions concerning tobacco dose and time since cessation, but the number of cases was too small in these sub-groups in order to allow for separate analysis.

Statistical methods

All participants in The Malmö Preventive Project were followed from baseline until a diagnosis of pancreatic cancer, death, or end of follow-up, 31 Dec. 2004. Mean follow-up was 22.1 years and the total number of person-years was 739,612.73. The incidence of pancreatic cancer was calculated per 100,000 person-years in different categories of studied exposures. Cox's proportional hazards analysis was used to estimate relative risks (RR) with a 95% confidence interval (CI). In the adjusted analysis, age at diagnosis was entered as a continuous factor and sex, smoking status, alcohol consumption category (Mm-MAST), γ-GT, body mass index and weight gain were entered as categorical variables. To adjust for alcohol consumption the Mm-MAST score was chosen, since it may be a more specific marker of alcohol consumption than γ-GT.

The relative risk for pancreatic cancer related to smoking and alcohol intake was furthermore analyzed in different strata of smoking, alcohol consumption, BMI and weight gain in order to detect modifying effects. Combining different levels of smoking and alcohol consumption required comparisons of groups with a limited number of cases, and some of these analyses used a dichotomized variable on alcohol consumption and γ-GT. That is, high/intermediate vs. low according to Mm-MAST, and GT-quartile 4 vs. GT-quartile 1-3. Interaction between smoking, alcohol and BMI was analyzed by entering one covariate multiplied by the other as an interaction term. A p-value of < 0.05 was considered to be indicative of a statistically significant interaction. All statistical calculations were performed using the software SPSS 14.0.

Results

Co-variation between potential risk factors

A breakdown of mean age, gender, and distribution of potential risk factors at baseline is given in table 1. The two methods used to estimate drinking habits co-varied to a large extent. The highest Mm-Mast category, as compared to the other two Mm-MAST categories, had a high proportion of the highest γ-GT category, and vice versa. Current smokers reported high alcohol consumption, measured according to both methods. Subjects in the highest category of γ-GT were more often obese as compared to the lowest γ-GT quartile. Contrary to this, there were no large differences between different Mm-MAST categories with regard to BMI. Current smokers were leaner than never and former smokers and a previous weight gain were most common among former smokers, table 1. There was a high correlation between self-reported weight gain and overweight/obesity. Among subjects reporting a previous weight gain, 79% had a BMI > 25, as compared to 34% among subjects who reported no weight gain (not shown in table).

Alcohol

High alcohol consumption, defined according to both Mm-MAST and γ-GT levels, was positively associated with pancreatic cancer, although the risk associated with the highest Mm-MAST category did not reach statistical significance, table 2.

When the fourth γ-GT-quartile was combined with a high alcohol consumption, defined as intermediate/high according to Mm-MAST, in a new covariate, this group had a RR of 2.41 (1.51-3.82) as compared to subjects with low alcohol consumption, i.e. low consumption according to Mm-MAST and γ-GT values in quartiles 1, 2 or 3 (not shown).

The risk of pancreatic cancer was high in the second and the fourth γ-GT-quartile among lean subjects, table 3. Apart from this, no large differences were seen in relation to different BMI categories. High alcohol consumption (measured using both the Mm-MAST and γ-GT) was associated with an increased risk in subjects that reported weight gain. However, several of the stratified analyses included only a few cases and the corresponding confidence intervals were wide.

A high Mm-MAST score was associated with pancreatic cancer in former smokers and a high γ-GT-quartile was associated with a high risk in current smokers, table 4. There were no statistically significant interaction between alcohol and BMI, alcohol and weight gain or between alcohol and smoking, table 3 and 4.

Smoking

Current smoking was associated with pancreatic cancer as compared to never smokers, table 2. There was a tendency towards an increasing risk in subjects who smoked the highest amount of cigarettes / day. When γ-GT was used instead of Mm-MAST category in order to adjust for alcohol consumption, all results were similar. Current smoking was positively

associated with the risk of pancreatic cancer in every strata of BMI and weight gain. In the group of obese subjects (BMI >30), the risk was even higher with an RR of 7.45 (1.65-33.64), table 3.

A positive association was found between former smoking and the risk of pancreatic cancer and the risk increased with time since smoke cessation, table 2. Furthermore, the risk of pancreatic cancer in former smokers was especially high in overweight subjects as compared to participants with a BMI < 25. Former smoking was associated with a slightly higher risk in subjects who had gained weight, as compared to subjects that had not, but this relation did not reach statistical significance, table 3.

Concerning the risk of pancreatic cancer, there were no statistically significant interaction between smoking and any of the other exposures, i.e. alcohol consumption, BMI or weight gain, table 3 and 4.

Discussion

An association between different measurements of high alcohol consumption and pancreatic cancer was found in this population-based prospective cohort study. This association may be even higher in subjects reporting a previous weight gain. Moreover, this study confirms previous findings on the positive association between smoking and pancreatic cancer, and indicates that obese current smokers may have a very high risk for pancreatic cancer. However**,** there are several methodological issues that have to be considered.

Regarding alcohol consumption there were no questions on absolute amounts of alcohol intake. The questionnaire was designed to detect alcohol addiction using questions about attitudes and customs, i.e. it focused on behaviour rather than quantity. However, other studies have shown that Mm-MAST is a valid tool in order to identify both heavy drinking and alcoholism [18]. ϒ-GT has previously been found to be a useful marker of alcohol

consumption [21,22]. One aspect of γ-GT is that these levels may be affected by several conditions such as obesity, medications, hepatic or biliary conditions and insulin resistance. Unfortunately, only obesity could be adjusted for in the present analysis. Nevertheless, γ-GT is considered a useful tool in order to identify excessive drinkers and it has been proved a useful determinant for alcohol related co-morbidities as reported by Kristenson et al [18]. In the present study we found a strong co-variation between Mm-MAST and γ-GT-quartile, table 1, which indicates that γ-GT is a useful tool for identification of heavy drinkers and alcoholics.

Smoking habits according to the questionnaire has previously been compared to plasma levels of carboxyhaemoglobin, showing a good agreement between these measurements [23].

For the validity of self-reported weight gain, our study showed a high correlation between a positive answer and a high body mass index, and a negative answer and a low body mass index. This may indicate a high validity of information on weight gain as the same association has been shown by other authors that have analyzed self-reported information on weight gain as compared to BMI [24].

For all measurements, there is one important limitation; exposure was only measured once; at baseline examination. The individuals could have changed their lifestyle during the follow-up period. Regarding smoking, the overwhelming majority of never smokers probably continued to be never smokers, as it is not likely to take-up smoking after the age of 30. However, some current smokers have probably given-up smoking, and this would have lead to an under-estimation of the risk associated with current smoking, and the true risk in this group may be even higher than the observed.

How or if alcohol habits vary over time and by age, is unclear. According to official statistics and public health reports [25], alcohol consumption has increased in Sweden during

the last decades, and in the same time the proportion of strict teetotallers has declined, especially among men and women over 45 years. If these changes can be applied to our cohort, we should expect higher alcohol consumption over time, than reflected in the Mm-MAST questionnaire, and in the γ-GT values at baseline, and thereby an underestimation of the true risk associated with high alcohol intake.

Approximately 71% of those who were invited to participate in the Malmö primary preventive project did attend. It may be difficult to apply observed incidence rates and absolute risks from this study to the general population. However, we consider that internal comparisons and calculations of relative risks are less sensitive to a potential selection bias.

Studies of pancreatic cancer are probably not prone to be affected by a potential detection bias. The tumor is highly aggressive, most patients that are diagnosed with pancreatic cancer die within a year and the 5 year survival rate is less than 5% [26].

The analysis in this study of single potential risk factors were adjusted - or stratified for other potential risk factors for pancreatic cancer. Hence, confounding due to these factors was probably a limited problem. Other factors that have previously been associated with pancreatic cancer include race, dietary- and nutritional factors, pre-existing disease (e.g. diabetes) and genetic factors[1]. Another possible confounder is chronic pancreatitis, which is a well-known risk factor for pancreatic cancer [12,27,28]. However, according to Otsuki et al [28] chronic pancreatitis may be the link between high alcohol consumption and pancreatic cancer, and if this is true, chronic pancreatitis should not be considered as a confounder. Still, a limitation of the present study was that there was no information on these factors.

Several case-control and prospective cohort studies have reported inconsistent results concerning whether or not alcohol is associated with pancreatic cancer. Only a few studies found a positive association [5-7,11,14,15]. The majority of these studies were cohort studies and only two case-control studies found a positive association and only in heavy drinking men

[6] and in heavy drinking blacks of the USA [11]. The cohort studies generally showed a stronger association between moderate alcohol consumption and the risk for pancreatic cancer [5,7,14,15].

Most previous studies have failed to show any association between obesity and pancreatic cancer. A meta-analysis of 14 studies on obesity and pancreatic cancer from 2003 estimated a 19% increase in risk of pancreatic cancer in obese individuals compared to those with a normal body weight [29]. In this paper we did not show any statistically significant increase, but the number of cases in the obese group (BMI>30) was small. The present study indicates that obesity may affect the association between smoking and pancreatic cancer, considerably increasing the risk in both current and former smokers. For alcohol the results seemed to be inverse, as high alcohol consumption was associated with an increased risk of pancreatic cancer in lean individuals, but not in obese. Although BMI and weight gain co-varied, the highest risk associated with high alcohol consumption was seen among subjects that reported a previous weight gain. Considering the small sub-groups, wide confidence intervals and limited statistical power in these sub- analysis, these findings will have to be confirmed in future studies.

Recent reviews are consistent regarding the positive association between smoking and pancreatic cancer [1,30-32]. Nearly all published reports show that tobacco increases the risk of pancreatic cancer, usually with about a 2-fold increase, as compared to non-smokers. Furthermore, according to Lowenfels et al. [33] , the risk persists several years after smoking cessation, in former smokers. Our paper confirms these findings with an increased risk persisting more than 5 years after smoking cessation.

Smoking is thought to exert its carcinogenic effect indirectly via the bloodstream or via duodenal contents or bile. There are several routes through which tobacco carcinogens can act, and one potential mechanism is that of activation and progression of an inflammatory

response in the pancreas. This is supported by the observation that smoking is an independent risk factor for chronic pancreatitis and the development of diabetes mellitus in pancreatitis, two conditions which have been suggested as a risk factor for the disease [12,26,32-34].

Alcohol (i.e. ethanol) is not known to be a carcinogen, but might function as a promoter or co-carcinogen. Ethanol is metabolized into acetaldehyde, free radicals and fatty acid ethyl esters [32]. Acetaldehyde is a known carcinogen that can mediate inflammation and fibrosis through different pathways. It inhibits DNA repair and is known to directly injure pancreatic tissue [35]. Alcohol metabolism results in reactive oxygen production via P450 2E1, which not only causes cell damage, but also initiate a series of inflammatory cytokines [35]. Furthermore synergistic effects between the metabolism of ethanol and the activation of nitrosamines via cytochrome P450 2E1 have been reported [35-37]. It has been hypothesized that metabolic effects of alcohol can enhance pro-inflammatory and carcinogenic changes in chronic pancreatitis and diabetes mellitus, leading to pancreatic cancer [38].

Although there was only a weak positive association between BMI and pancreatic cancer in this study, there are several potential biological mechanisms that may link obesity and risk of pancreatic cancer. One is related to the fact that obesity leads to an abnormal glucose intolerance and hyperinsulinemia and that this has been proposed as the underlying mechanism explaining the positive association between diabetes mellitus and pancreatic cancer [9,39,40]. Considering that both smoking and alcohol may affect glucose metabolism and insulin sensitivity [12,41-43], and given the results in this study, it would be valuable to include information on additional metabolic factors in future studies.

In conclusion, this study reports an association between a high alcohol intakes, estimated both using a questionnaire concerning drinking habits and γ-GT, and the risk of developing pancreatic cancer. The risk appears to be higher in subjects reporting a previous weight gain. The previously established associated between smoking and pancreatic cancer

could be confirmed. The highest risk of pancreatic cancer related to smoking was found in obese subjects.

Acknowledgements

Financial support was received from The Einar and Inga Nilsson Foundation, The Malmö University Hospital Funds and Donations, The Malmö University Hospital Cancer Foundation, The Crawfoord Foundation, The Ernhold Lundström Foundation, and the Maggie Stephens Foundation.

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Table1. Distribution of potential risk factors as measured at baseline examination.

Factor	Category	Smoking status n (%)				Alcohol consumption* Mm-MAST category n (%)				γ-GT-quartile n (%)				
		Never	Current	Former	Missing	Low	Inter-mediate	High	Missing	1	2	3	4	Missing
Age (years)	Mean	45.4	44.8	48.1	52.7	46.4	44.3	42.3	49.9	43.1	45.1	46.5	48.3	46.6
Sex	Men	7391 (59.4)	11041 (74.4)	4012 (66.8)	0 (0.0)	9141 (56.8)	9092 (75.3)	2069 (90.4)	2142 (74.0)	3143 (34.9)	5417 (70.4)	6797 (81.9)	7045 (85.6)	42 (67.3)
	Women	5044 (40.6)	3809 (25.6)	1998 (33.2)	51 (100)	6951 (43.2)	2979 (24.7)	219 (9.6)	753 (26.0)	5867 (65.1)	2280 (29.6)	1506 (18.1)	1184 (14.4)	65 (60.7)
	Total	12435	14850	6010	51	16092	12071	2288	2895	9010	7697	8303	8229	107
Smoking status	Never					7469 (46.4)	3640 (30.2)	495 (21.6)	831 (28.7)	4232 (47.0)	2927 (38.0)	2751 (33.1)	2478 (30.1)	47 (43.9)
	Current					5808 (36.1)	6147 (50.9)	1520 (66.4)	1375 (47.5)	3138 (34.8)	3445 (44.8)	3992 (48.1)	4242 (51.5)	33 (30.8)
	Former					2815 (17.5)	2284 (18.9)	273 (11.9)	638 (22.0)	1617 (17.9)	1311 (17.0)	1554 (18.7)	1502 (18.3)	26 (18.0)
	Missing					0	0	0	51 (1.8)	23 (0.3)	14 (0.2)	6 (0.1)	7 (0.1)	1 (0.1)
Alcohol* : Mm-MAST	Low	7469 (60.1)	5808 (39.1)	2815 (46.8)	0 (0)					5427 (60.2)	3969 (51.6)	3661 (44.1)	2980 (36.2)	55 (51.4)
	Intermediate	3640 (29.3)	6147 (41.4)	2284 (38.0)	0 (0)					2642 (29.3)	2860 (37.2)	3254 (39.2)	3291 (40.0)	24 (22.4)
	High	495 (4.0)	1520 (10.2)	273 (4.5)	0 (0.0)					282 (3.1)	398 (5.2)	607 (7.3)	996 (12.1)	5 (4.7)
	Missing	831 (6.7)	1375 (9.3)	638 (10.6)	51 (98.1)					659 (7.3)	470 (6.1)	781 (9.4)	962 (11.7)	23 (8.7)
γ-GT-quartile (μkat/L)	1 (<0.29)	4232 (34.2)	3138 (21.2)	1617 (27.0)	23 (46.0)	5427 (33.8)	2642 (21.9)	282 (12.4)	659 (22.9)					
	2 (0.29-0.41)	2927 (23.6)	3445 (23.3)	1311 (21.9)	14 (28.0)	3969 (24.7)	2860 (23.7)	398 (17.4)	470 (16.4)					
	3 (0.41-0.63)	2751 (22.2)	3992 (26.9)	1554 (26.0)	6 (12.0)	3661 (22.8)	3254 (27.0)	607 (26.6)	771 (27.2)					
	4 (>0.63)	2478 (20.0)	4242 (28.6)	1502 (25.1)	7 (14.0)	2980 (18.6)	3291 (27.3)	996 (43.6)	962 (33.5)					
	Missing	47 (0.4)	33 (0.2)	26 (0.4)	1 (2.0)	55 (0.3)	24 (0.2)	5 (0.2)	23 (0.8)					
BMI (kg/m^2)	< 20	686 (5.5)	1375 (9.3)	271 (4.5)	1 (2.0)	1227 (7.6)	829 (6.9)	137 (6.0)	140 (4.8)	990 (42.6)	5649 (31.9)	2005 (18.7)	363 (14.9)	3 (13.0)
	≥20–25	6553 (52.7)	8219 (55.3)	2983 (49.6)	19 (37.3)	8410 (52.3)	6677 (55.3)	1228 (53.7)	1459 (50.4)	603 (25.9)	4525 (25.5)	2145 (20.0)	411 (16.8)	4 (17.4)
	≥25–30	4122 (33.1)	4378 (29.5)	2257 (37.6)	18 (35.3)	5080 (31.6)	3875 (32.1)	790 (34.5)	1030 (35.6)	442 (19.0)	4275 (24.1)	2970 (27.7)	593 (24.2)	5 (21.7)
	≥ 30	1062 (8.5)	871 (5.9)	495 (8.2)	13 (25.5)	1359 (8.4)	688 (5.7)	133 (5.8)	261 (9.0)	287 (12.3)	3243 (18.3)	3593 (33.5)	1066 (43.6)	5 (21.7)
	Missing	12 (0.1)	7 (0.0)	4 (0.1)	0 (0)	16 (0.1)	2 (0.0)	0 (0.0)	5 (0.2)	9 (0.4)	49 (0.3)	32 (0.3)	11 (0.5)	6 (26.1)
Weight gain >10 kg	No	6564 (52.8)	8705 (58.6)	3878 (64.5)	0 (-)	9821 (61.0)	6215 (54.0)	927 (40.5)	1885 (65.1)	6159 (68.4)	4402 (57.2)	4623 (55.7)	3902 (47.4)	62 (57.4)
	Yes	2685 (21.6)	2940 (19.8)	2129 (35.4)	0 (-)	3809 (23.7)	2530 (21.0)	478 (20.9)	937 (32.4)	1695 (18.8)	1440 (18.7)	1879 (22.6)	2702 (32.8)	38 (23.3)
	Missing	3185 (25.6)	3208 (21.6)	3 (.0)	51 (100)	2462 (15.3)	3026 (25.1)	883 (38.6)	73 (2.5)	1156 (12.8)	1855 (24.1)	1801 (21.7)	1625 (19.7)	7 (6.5)

*Alcohol consumption according to Mm-MAST: Malmö modification of the brief Michigan Alcoholism Screening Test.

Table 2. Incidence and relative risk of pancreatic cancer in different exposure categories.

Factor	Category	Individuals (n)	Cases (n)	Incidence/ 100 000 person-years	RR (95% CI)	RR‡ (95% CI)
Smoking status	Never	12 435	38	13.7	1.00 (ref.)	1.00 (ref.)
	All Current	14 850	107	32.7	2.37 (1.64-3.44)	2.34 (1.60-3.43)
	≤ 20 cigarettes / day	6624	46	31.4	2.27 (1.48-3.49)	2.25 (1.45-3.50)
	>20 cigarettes / day	4979	37	34.8	2.59 (1.65-4.08)	2.56 (1.60-4.09)
	missing dose	3247	24	32.2	2.27 (1.36-3.78)	2.31 (1.37-3.89)
	Former	6010	38	28.4	2.05 (1.31-3.22)	1.61 (1.02-2.55)
	abstinence ≤5 years	1724	8	20.3	1.44 (0.67-3.08)	1.23 (0.57-2.67)
	abstinence >5 years	3756	30	36.7	2.68 (1.66-4.33)	2.00 (1.21-3.29)
	missing	530	0	0	-	-
	Missing	51	0	0	-	-
Alcohol* Mm-MAST*	Low	16 092	71	20.1	1.00 (ref.)	1.00 (ref.)
	Intermediate	12 071	78	28.7	1.41 (1.03-1.95)	1.50 (1.07-2.08)
	High	2288	14	27.9	1.38 (0.78-2.45)	1.58 (0.88-2.86)
	Missing	2895	20	31.2	1.41 (0.83-2.37)	1.06 (0.62-1.79)
	Trend (over categories)	30451	183	24.1	P-value‡ =0.050	P-value‡ =0.020
γ-GT - quartile	1 (<0.29)	9010	32	16.8	1.00 (ref.)	1.00 (ref.)
	2 (0.29-0.41)	7697	43	24.7	1.40 (088-2.21)	1.52 (0.95-2.45)
	3 (0.41-0.63)	8303	40	20.9	1.16 (0.73-1.85)	1.24 (0.75-2.03)
	4 (≥0.63)	8229	68	37.4	2.10 (1.38-3.20)	2.15 (1.34-3.44)
	Missing	107	0	0	-	-
	Trend (multiples of 0.1)	33239	183	24.8	1.01 (1.006-1.02)	1.01 (1.005-1.02)
BMI (kg/m^2)	< 20	2333	10	19.1	0.76 (0.40-1.45)	0.84 (0.44-1.61)
	20–<25	17774	101	25.4	1.00 (ref.)	1.00 (ref.):
	25–<30	10775	54	22.6	0.89 (0.64-1.23)	0.83(0.60-1.16)
	≥ 30	2423	18	36.1	1.50 (0.91-2.47)	1.38(0.83-2.28)
	Missing	23	0	0	-	-
	Trend (continuous)	33305	183	24.8	1.05 (1.01-1.09)	1.04 (0.995-1.08)
Weight gain >10 kg	No	19148	118	27.7	1.00 (ref.)	1.00 (ref.)
	Yes	7754	52	32.2	1.21 (0.88-1.68)	1.07 (0.77-1.48)
	Missing	6444	13	8.6	0.30 (0.17-0.53)	0.65 (0.34-1.27)

*Alcohol consumption according to Mm-MAST:: Malmö modification of the brief Michigan Alcoholism Screening Test.
‡ Adjusted for age, sex, smoking status, Mm-MAST category (Mm-MAST is not adjusted for γ-GT and γ-GT is not adjusted for Mm-MAST) and BMI (weight gain not adjusted for BMI).

Table 3. Relative risk of pancreatic cancer associated smoking, alcohol consumption and γ-GT in different categories of BMI and weight gain

Factor	Category	BMI (kg/m²)								Weight gain > 10 kg				
		< 25		25 – 30			≥ 30			No		Yes		
		Case (n)	RR‡ (95% CI)	Case (n)	RR‡ (95% CI)	Inter-action‡ p-value	Case (n)	RR‡ (95% CI)	Inter-action‡ p-value	Case (n)	RR‡ (95% CI)	Case (n)	RR‡ (95% CI)	Inter-action‡ p-value
Smoking status	Never	24	1.00 (ref.)	12	1.00 (ref.)		2	1.00 (ref.)		26	1.00 (ref.)	10	1.00 (ref.)	
	Current	70	2.05 (1.27-3.29)	24	2.03 (1.00-4.14)	0.79	13	7.45 (1.65-33.64)	0.72	72	2.11 (1.33-3.35)	24	2.13 (0.99-4.55)	0.87
	Former	17	1.16 (0.62-2.18)	18	2.20 (1.04-4.67)	0.26	3	3.01 (0.50-18.27)	0.32	20	1.19 (0.66-2.15)	18	1.96 (0.88-4.33)	0.26
	Missing status	0	-	0	-		0	-			-	0	-	
Alcohol* Mm-MAST	Low	44	1.00 (ref.)	20	1.00 (ref.)		7	1.00 (ref.)		50	1.00 (ref.)	18	1.00 (ref.)	
	Intermediate	47	1.42 (0.93-2.16)	25	1.74 (0.95-3.21)	0.71	6	1.35 (0.43-4.25)	0.67	50	1.43 (0.96-2.14)	21	1.63 (0.85-3.12)	0.67
	High	10	1.89 (0.93-3.84)	2	0.83 (0.19-3.66)	0.23	2	1.89 (0.36-9.89)	0.57	7	1.46 (0.65-3.27)	4	1.61 (0.53-4.89)	0.87
	Missing	10	0.86 (0.41-1.79)	7	1.23 (0.048-3.16)		3	1.93 (0.46-8.10)		11	0.71 (0.34-1.48)	9	1.82 (0.79-4.17)	
	Trend (over categories)	111	p-value‡ = 0.050	54	p-value‡ = 0.305		18	p-value‡ = 0.342		118	p-value‡ = 0.115	52	p-value‡ = 0.144	
γ-GT-quartile (μ-kat/L)	1 (<0.29)	22	1.00 (ref.)	8	1.00 (ref.)		2	1.00 (ref.)		26	1.00 (ref.)	5	1.00 (ref.)	
	2 (0.29-0.41)	33	1.83 (1.04-3.21)	9	1.20 (0.45-3.21)	0.31	1	0.35 (0.03-3.94)	0.24	33	1.59 (0.93-2.73)	6	1.31 (0.39-4.35)	0.74
	3 (0.41-0.63)	25	1.37 (0.75-2.53)	12	1.14 (0.43-2.99)	0.45	3	0.64 (0.09-4.27)	0.65	28	1.19 (0.67-2.13	10	1.62 (0.53-4.99)	0.66
	4 (>0.63)	31	2.22 (1.23-4.00)	25	2.04 (0.83-4.99)	0.49	12	1.31 (0.24-7.16)	0.90	31	1.60 (0.90-2.85)	31	3.61 (1.29-10.09)	0.17
	Missing	0	-	0	-		0	-		0	-	0		
	Trend (multiples of 0.1)	111	1.01 (1.005-1.02)	54	1.02 (1.003-1.04)		18	0.98 (0.90-1.06)		118	1.01 (1.001-1.02)	52	1.02 (1.008-1.02)	

*Alcohol consumption according to Mm-MAST: Malmö modification of the brief Michigan Alcoholism Screening Test.

‡ adjusted for age, sex, smoking status, and Mm-Mast category (Mm-MAST is not adjusted for γ-GT and γ-GT is not adjusted for Mm-MAST).

Table 4. Interaction between smoking, alcohol consumption and γ-GT in relation to relative risk

Factor	Smoking status			Alcohol consumption* Mm-Mast category		γ-GT (μkat/L)	
	Never	Current	Former	Low	Intermediate and high	< 0.63	> 0.63
	RR‡ (95% CI)			RR‡ (95% CI)		RR‡ (95% CI)	
Cases (n)	38	107	38	71	92	115	68
Never smoker				1.00 (ref.)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Current smoker				2.62 (1.52-4.48)	2.47 (1.32-4.63)	2.06 (1.31-3.24)	3.42 (1.66-7.07)
Interaction				–	p-value‡ = 0.96	–	p-value‡ = 0.26
Former smoker				1.32 (0.65-2.71)	2.25 (1.11-4.57)	1.71(1.00-2.93)	1.75 (0.73-4.20)
Interaction				–	p-value‡ = 0.24	–	p-value‡ = 0.88
Alcohol consumption* intermediate and high vs. low	1.31(0.63-2.72)	1.39 (0.91-2.12)	2.13 (1.05-4.32)				
Interaction	–	p-value‡ = 0.96	p-value‡ = 0.29				
High γ-GT ≥0.63 vs. <0.63 (μkat/L)	1.32 (0.60-2.90)	2.01(1.34-3.02)	1.21(0.59-2.48)				
Interaction	–	p-value‡ = 0.24	p-value‡ = 0.88				

*Alcohol consumption according to Mm-MAST: Malmö modification of the brief Michigan Alcoholism Screening Test.
‡ adjusted for age, sex, smoking status, BMI, and Mm-Mast category (Mm-MAST is not adjusted for γ-GT and γ-GT is not adjusted for Mm-MAST).