

Is tobacco a risk factor for chronic pancreatitis and alcoholic cirrhosis?

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Abstract

In a case control study alcohol intake and tobacco use were assessed between 1975 and 1987 in 103 male patients suffering from alcoholic cirrhosis of the liver, in 145 patients with chronic pancreatitis, and in 264 control subjects. The patients with chronic pancreatitis were significantly younger than the patients with cirrhosis (mean (SD) age 41.92 (2.4) v 60.9 (11.6) years). Among the patients with chronic pancreatitis, 94% were both smokers and drinkers compared with 83% of patients with cirrhosis of the liver. The relative risks for each disease were calculated by conditional multiple logistic regression. Whereas daily intake of alcohol was a major risk factor for both cirrhosis of the liver and chronic pancreatitis, smoking was significantly related only to the risk of having chronic pancreatitis. Moreover, the mean age at onset of pancreatitis was lower among smokers.

In 1878 Friedreich¹ was the first to suspect the role of heavy alcohol consumption in the aetiology of pancreatitis. His observation has since been supported by many clinical studies.²⁻⁴ Later, Durbec and Sarles showed that the logarithm of the risk of developing alcoholic chronic pancreatitis was linearly correlated with the mean daily alcohol consumption.⁴ More recently, Yen *et al*⁵ pointed out that chronic pancreatitis was strongly associated not only with alcohol consumption but also with cigarette smoking, the apparent effect of tobacco being dissociated from the effect of alcohol. Lowenfels *et al*⁶ showed that in the male American Indian population smoking was more frequent among chronic pancreatitis patients than among patients with alcoholic liver cirrhosis. Smoking and drinking, however, generally coexist as social habits.⁷ The aim of the present case-control study was to investigate the relative contributions of alcohol and tobacco as risk factors for chronic pancreatitis and cirrhosis of the liver.

Methods

In 1972 a standardised questionnaire on radiological and biological symptoms and nutritional state was prepared for use in further studies.⁸ It has been used in our department for 147 new cases of chronic pancreatitis diagnosed between 1975 and 1987. The diagnosis was based on (i) pancreatic stones (calcifications) visible on x ray films of the abdomen (91 of 147 patients), (ii) on typical pancreatitis pain associated with modifications of pancreatic ducts at endoscopic retrograde cholangiopancreatography (94 of 147

patients),⁹ and on exocrine pancreatic insufficiency estimated from duodenal juice collected after injection of secretin and cholecystokinin (81 of 147 patients).

Between 1980 and 1987 the same questionnaire was used for 173 patients presenting with alcoholic cirrhosis of the liver. The diagnosis of alcoholic cirrhosis was based on clinical, biological, histological (liver biopsy), and nutritional data. Nineteen patients with cirrhosis were excluded because of missing data on alcohol consumptions and tobacco use. Seven patients with both cirrhosis and chronic pancreatitis were also excluded. Thus 103 men with alcoholic cirrhosis were studied. Between 1985 and 1988 a control group was selected from interviews carried out during systematic medical examinations for the French social security system. Cases and control subjects were investigated by specially trained dietitians on alcohol, smoking, and dietary habits. Particular attention was given to the duration and intensity of smoking and to the age at starting and stopping smoking. Questions were asked about the amount, frequency, and duration of alcohol consumption at and before the onset of the disease. We only took into account the patients who provided full information on their drinking and smoking habits (145 chronic pancreatitis, 147 cirrhosis of the liver, 264 control subjects). Daily alcohol consumption was expressed as ml/day, tobacco use as average grams of tobacco per day and in kg before the onset of the disease.

Statistical analyses were performed with Student's *t* test, the Mann-Whitney U test, the Kruskal-Wallis one way analysis of variance on ranks, and Spearman's rank coefficients. We used conditional multiple logistic regression to estimate the relative risks of chronic pancreatitis or cirrhosis of the liver for each variable (daily consumption of alcohol or of tobacco use, lifetime use of tobacco, body mass index).¹⁰ Cases of chronic pancreatitis or of cirrhosis were matched to one or several control subjects in 10 year age groups to compensate in this model for the age difference between patients with chronic pancreatitis and cirrhosis of the liver and control subjects.¹⁰ So the logarithm of the relative risk was expressed as a linear combination of each variable studied and of parameters estimated by method of maximum conditional likelihood. The variables were examined for separate associations with chronic pancreatitis or cirrhosis, for confounding factors, and for interaction. Statistical significance was tested for by comparing deviance differences with log likelihood ratio tests.¹¹ Computer software (Computer Fortran 5 program)¹² was a generous gift of J H Lubin. We showed that studying our patients and control subjects at different time periods would not

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TABLE I Age, daily intake of alcohol, and cigarette use at different periods (mean (SD)) among patients with chronic pancreatitis (CP), control subjects (C), and patients with liver cirrhosis (LC)

	1975-80	1981-5	1986-7	p
No of patients:				
CP	57	65	10	
C		167		
LC	0	70	33	
Age (years):				
CP	41.2 (8.6)	42.9 (11.7)	39.1 (10.4)	=0.44
C		57.9 (13.4)		
LC		61.9 (12)	58.9 (10)	=0.23
Alcohol intake (ml/day):				
CP	191.0 (155.5)	172.9 (107.2)	188.0 (100.2)	=0.72
C		38.6 (48.2)		
LC		171.5 (97.6)	170.4 (114)	=0.96
Tobacco use (g/day):				
CP	272. (15.2)	27.1 (16.2)	24.0 (9.9)	=0.82
C		15.7 (18)		
LC		25.2 (21)	25.4 (20.7)	=0.95
Body mass index (kg/cm):				
CP	21.2 (2.8)	20.9 (2.9)	21.0 (2.8)	=0.90
C		24.9 (3.9)		
LC		24.1 (4.6)	25.2 (4.9)	=0.24

TABLE II Distribution of patients with chronic pancreatitis (CP), control subjects (C), and of patients with cirrhosis (LC) by sex, cigarette use, and alcohol consumption (all values mean (SD) are given for men only)

	CP	C	LC
Number:			
Total	145	264	147
Men	132	167	103
Women	13	97	44
Age (years):	41.9 (10.4)	57.9 (13.4)	60.9 (11.6)
CP v C			p<0.001
CP v LC			p<0.001
Alcohol intake (ml/day):	182.6 (129.2)	38.6 (48.2)	171.2 (102.6)
CP v C			p<0.001
CP v LC			p=0.46
Tobacco use (g/day):	26.9 (15.3)	15.7 (18)	25.2 (20.8)
CP v C			p=0.48
CP v LC			p=0.48
% Drinkers:	100	67	100
CP v C			p<0.01
CP v LC			p<0.01
% Smokers:	94	61	83.5
CP v C			p<0.01
CP v LC			p<0.01
Body mass index (kg/cm):	21.1 (2.9)	24.9 (3.9)	24.4 (4.7)
CP v C			p<0.001
CP v LC			p<0.001

TABLE III Comparison between men with chronic pancreatitis (CP) (n=132) and male control subjects (C) (n=167) by age at onset of disease, alcohol consumption, and cigarette use (mean (SD))

	Smokers		Non-smokers	
	CP	C	CP	C
No of patients	125	102	7	65
Age (years):	41.35 (9.92)	47.09 (9.01)	52.14 (14.02)	47.42 (7.18)
CP v C				p=0.54
CP v CP			p=0.03	
C v C			p=0.49	
Alcohol (ml/day):	185.1 (130)	43.11 (47.76)	138.7 (114)	31.6 (48.42)
CP v C				p=0.001
CP v CP			p=0.28	
C v C			p=0.13	
Tobacco (g/day):	28.4 (14.3)	25.73 (16.42)	0	0
CP v C				
Tobacco (kg/l):	235.4 (159.7)	238.5 (201.76)	0	0
CP v C				
Body mass index (kg/cm):	21.1 (2.9)	24.95 (3.84)	21.1 (2.1)	24.69 (3.07)
CP v C				p<0.01
CP v CP			p=0.80	
C v C			p=0.93	

Student's t test between C and CP in each group; Mann-Whitney U test between CP in the two groups.

influence our results (Table I). For descriptive purposes, data have been expressed as mean (SD).

Results

WOMEN

We did not take women into account in this case-

control study because of the small number of women affected by chronic pancreatitis (13 of 145). Such a small number does not allow us to draw any definite conclusion concerning women. So daily intake of alcohol and tobacco use were only studied for 132 male patients with chronic pancreatitis, 103 male patients with cirrhosis of the liver, and 167 male control subjects (Table II).

CONTROL SUBJECTS

Among the 264 control subjects, 167 were men; 112 men (67%) were drinkers and 102 men (61%) were smokers (Table II); 76 (67.8%) were both drinkers and smokers. Smokers were not found to be different from non-smokers for age, daily intake of alcohol, and body mass index (Table III).

After classifying subjects by smoking habits (none, <10 g/day, 10-20 g/day, >20 g/day) no relation between tobacco use and alcohol consumption was found among the 167 male control subjects (Table IV).

After classifying subjects by daily intake of alcohol, however, the heavier drinkers were found to be the heavier smokers (Table V). The percentage of heavy male drinkers (more than 100 ml/day) was higher among chronic pancreatitis patients (77.3% of total) than among control subjects (10.2% of total). So in controls the heavier drinkers were also the heavier smokers, but the opposite was not true.

No correlations were found between age and tobacco use or between age and alcohol consumption using non-parametric correlations (Table VI).

CHRONIC PANCREATITIS

Among the 145 patients with chronic pancreatitis 132 were men (91%) and 13 were women (9%); the mean (SD) age of the men was 41.92 (2.4) years (Table II). Alcohol was found to be the most common aetiological factor: 132 patients with chronic pancreatitis were drinkers (100%); 125 (94.4%) used tobacco.

Among the 132 men, 125 were both drinkers and smokers (94.7%) and seven only drinkers. The mean age at the time of diagnosis was significantly lower in smokers (41.35 (9.9) years) than in non-smokers (52.14 (14.02) years) (Table III). Body mass index and daily alcohol consumption were the same among smokers and non-smokers (Table III).

After classifying patients by smoking history (none, <10 g/day, 10-20 g/day, >20 g/day) a significant relation between tobacco use and daily intake of alcohol (p=0.036) was observed (Table IV). Moreover, there was a reciprocal relation between alcohol consumption and daily tobacco use when the sample was stratified according to alcohol consumption (Table V). Thus, the heavier drinkers were also the heavier smokers, and vice versa.

Table VI shows that there is no linear correlation between the age at onset of disease and tobacco use, whereas there is a significant slight negative correlation between age at onset of disease and daily intake of alcohol.

TABLE IV Daily intake of alcohol in male control subjects (C) (n=167) and in male patients with chronic pancreatitis (CP) (n=132) and cirrhosis (LC) (n=103) after stratifying by smoking history (mean (SD))

	Tobacco (g/day)				p
	0	0-10	10-20	>20	
% of patients:					
CP	5.3	6.8	44.7	43.2	
C	39.0	10.0	26.0	24.0	
LC	16.5	9.7	36.9	36.9	
Alcohol (ml/day):					
CP	138.7 (43.1)	97.3 (17.4)	191.8 (19.1)	192.0 (15.4)	=0.03
C	31.6 (6.0)	42.4 (10.0)	45.6 (6.3)	40.7 (8.8)	=0.48
LC	203.6 (75.1)	124.1 (54.6)	164.3 (105.1)	176.1 (116.9)	=0.03

Standard analysis of variance.

TABLE V Daily tobacco use in male control subjects (C) (n=167) and in male patients with chronic pancreatitis (CP) (n=132) and cirrhosis (LC) (n=103) after stratifying by alcohol consumption (mean (SD))

	Alcohol (ml/day)				p
	0	0-50	50-100	>100	
% of patients:					
CP	0	5.3	17.4	77.3	
C	33	34.7	22.1	10.1	
LC	0	5.8	23.3	70.9	
Tobacco (g/day):					
CP	-	13.3 (4.2)	24.6 (3.3)	28.3 (1.5)	<0.01
C	12.8	17.3 (2.1)	11.9 (2.4)	27.9 (5.8)	=0.008
LC	-	33.3 (16.3)	20.8 (10.4)	26.0 (23.4)	=0.31

Standard analysis of variance.

TABLE VI Correlation between age and tobacco use or alcohol consumption in male control subjects and male patients with chronic pancreatitis

Correlation	Alcohol (g/day)	Tobacco (g/day)
Age (years) of control subjects (n=112)	r = 0.15 p = 0.10	r = 0.04 p = 0.64
Age (years) of patients (n=132)	r = -0.24 p = 0.005	r = -0.07 p = 0.38

Spearman's rank correlations.

TABLE VII Relative risk of alcohol (g/day) and tobacco (g/day or kg) in chronic pancreatitis

	Variables			
	β	SE	Z	RR
Alcohol (ml/day)	0.30 10 ⁻² *	0.49 10 ⁻³	6.125 p<0.001	1.003*
Tobacco (g/day)	0.15 10 ⁻¹ *	0.44 10 ⁻²	3.38 p<0.001	1.015*
Tobacco (kg/l)	0.67 10 ⁻² *	0.23 10 ⁻²	2.92 p<0.003	1.007*
Alcohol (g/day)	0.27 10 ⁻² *	0.51 10 ⁻³	5.37 p<0.001	1.003*
Tobacco (g/day)	0.99 10 ⁻² *	0.47 10 ⁻²	2.107 p<0.035	1.010*
Alcohol (g/day)	0.27 10 ⁻² *	0.51 10 ⁻³	5.35 p<0.001	1.003*
Tobacco (kg/l)	0.11 10 ⁻⁵ *	0.46 10 ⁻⁶	2.46 p<0.0014	1.0*
Alcohol (g/day)	0.27 10 ⁻² *	0.51 10 ⁻²	5.37 p<0.001	1.003*
Tobacco (g/day)	0.90 10 ⁻² *	0.44 10 ⁻³	1.90 p<0.057	1.005*
Tobacco (kg/l)	0.54 10 ⁻² *	0.26 10 ⁻²	2.03 p<0.042	1.005*

*p<0.05, log RR = Σ_{i=1,n} β_i(X_i' - X_j); β: estimated parameter; SE: standard error; Z: ratio of β to its standard error.

Daily intake of alcohol, daily tobacco use, and lifetime tobacco use separately seemed to be risk factors for pancreatitis (Table VII). When the effects of daily alcohol intake and daily tobacco use or lifetime use were studied simultaneously – that is, without interaction between these vari-

ables – they still both appeared as risk factors for chronic pancreatitis (Table VII): in this case alcohol habit (χ²=28.84, 1 degree of freedom, df) was more important as a risk factor than smoking habit (χ²=4.41, 1 df) (Table VII). These variables, however, have a multiplying effect on the relative risk of pancreatitis, since the logarithm of this relative risk is a linear combination of the variables studied.

ALCOHOLIC CIRRHOSIS

Altogether, 103 men with alcoholic cirrhosis of the liver were studied. The mean (SD) age at onset of disease was 60.9 (11.6) years. The mean (SD) daily alcohol consumption was 171.2 (102.6) ml/day and mean (SD) tobacco use was 25.2 (20.8) g/day. The mean (SD) body mass index was 24.4 (4.7) (Table II). Eighty six patients (83.5%) were both drinkers and smokers. Their mean tobacco use was 30.23 (19.2) g/day. Seventeen patients were drinkers only. Age at onset of disease, body mass index, and daily alcohol consumption were the same among smokers and non-smokers (Table VIII).

After classifying patients by smoking history (none, <10 g/day, 10-20 g/day, >20 g/day), a significant relation between tobacco use and daily intake of alcohol (p=0.037) was found (Table IV). No relation was found, however, between alcohol consumption and daily tobacco use when the sample was stratified by alcohol consumption (Table V). Thus in cirrhosis of the liver the heavier smokers were the heavier drinkers, but not the opposite.

Only daily alcohol intake seemed to be a risk factor for alcoholic cirrhosis (Table IX). When daily alcohol intake and tobacco use were studied simultaneously – that is, without interaction between these variables – daily tobacco use no longer appeared as a risk factor for alcoholic cirrhosis.

TABLE VIII Comparison by age, daily alcohol intake, and body mass index, between smokers and non-smokers with alcoholic cirrhosis

	Smokers	p	Non-smokers
No of patients	86		17
Age (years) at onset of disease	61.3 (11.5)	p=0.52	59.3 (12.3)
Alcohol (ml/day) (mean (SD))	164.8 (106.4)	p=0.15	203.6 (75.1)
Body mass index (kg/cm) (mean (SD))	24.3 (4.5)	p=0.55	25.0 (5.8)

TABLE IX Relative risk of alcohol (g/day) and tobacco (g/day) in alcoholic cirrhosis

	Variables			
	β	SE	Z	RR
Alcohol (ml/day)	0.51 10 ⁻² *	0.62 10 ⁻³	8.251 p<0.001	1.005*
Tobacco (g/day)	0.10 10 ⁻¹ *	0.43 10 ⁻²	2.31 p<0.021	1.010*
Alcohol (ml/day)	0.51 10 ⁻² *	0.67 10 ⁻³	7.62 p<0.001	1.005*
Tobacco (g/day)	0.17 10 ⁻² †	0.47 10 ⁻²	0.36 p<0.71	1.002†

*p<0.05; †not significant. β: estimated parameter; SE: standard error; Z: ratio of β to its standard error.

Discussion

Smoking and drinking are social habits that generally coexist.⁷ In the United States Yen *et al*⁵ and Lowenfels *et al*⁶ first suggested that smoking is a risk factor for alcoholic pancreatitis in male patients. However, smoking and drinking habits differ world wide. For example, 63% of male control subjects in the United States⁵ and 33% in France⁷ were non-smokers. Therefore, the aim of this case-control study was to investigate the relative contribution of tobacco as a risk factor among men in France in two alcohol related diseases – chronic pancreatitis and cirrhosis of the liver. We may first observe that the epidemiological characteristics of our three samples (patients with chronic pancreatitis and cirrhosis of the liver and control subjects) are similar to those reported in previous studies. In our chronic pancreatitis group the sex ratio (91% male), age at onset of the disease (41.9 years), and daily alcohol consumption are the same as in other French studies.¹³⁻¹⁴ The same is true for sex ratio (70% of males) and daily consumption of alcohol in cirrhosis.¹⁵⁻¹⁶ The age at diagnosis of cirrhosis of the liver is the same in our sample as in previous French and Swiss studies,¹⁵⁻¹⁷ but is higher than in previous German¹⁸ or American^{6,19} studies. The proportion of smokers and drinkers, and the mean daily consumption of alcohol and tobacco use in our control sample is the same as in the previous large epidemiological studies,^{7,20-21} but differs from that reported in the American study of Yen *et al*.⁵ This emphasises the differences in smoking and drinking habits in various countries.

It is worth noting that the relation between alcohol and tobacco is not the same in chronic pancreatitis, cirrhosis, and control subjects. In chronic pancreatitis heavy drinkers develop pancreatitis sooner and the average daily consumption of alcohol and tobacco use are closely correlated. This is not found in cirrhosis, where only heavy smokers are heavy drinkers, nor in control subjects where heavy drinkers are heavy smokers. This may explain the finding that although average daily use of tobacco and alcohol are the same in cirrhosis and chronic pancreatitis, tobacco appears as risk factor only for chronic pancreatitis. This conclusion agrees with those of Yen *et al* and Lowenfels *et al*, but all of these epidemiological studies are case-control studies where populations showed different epidemiological characteristics.^{5,6} In a case-control study, rather than an on-going study, bias can be introduced and conclusions must be carefully drawn. However, we try to show in Table I that epidemiological features in chronic pancreatitis and in liver cirrhosis did not change

during our study. There is also a potential for bias in the selection of the control subjects. As we saw later, our control subjects do not seem much different from the control subjects in other large epidemiological French or European studies.^{7,20-21}

Therefore, further epidemiological studies, especially on-going studies, are mandatory to study the relation between alcohol, tobacco, and nutritional data in these two diseases.

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