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Tobacco smoking, alcohol consumption and pancreatic cancer risk: A case-control study in Italy

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ABSTRACT

In Italy, pancreatic cancer accounts for approximately 5% of cancer-related deaths. Tobacco smoking is the major established risk factor for this cancer, whereas the role of alcohol consumption is open to debate.

Between 1991 and 2008, we conducted a hospital-based case-control study on pancreatic cancer in northern Italy. Cases were 326 patients (median age 63 years) with incident pancreatic cancer admitted to major general hospitals. Controls were 652 patients (median age 63 years) with acute non-neoplastic conditions admitted to the same hospital network of cases. Multiple logistic regression was used to estimate the odds ratios (OR) and the corresponding 95% confidence intervals (CI).

Pancreatic cancer was associated to current smoking (OR = 1.68; 95% CI: 1.13–2.48), and the risk rose with increasing number of cigarettes/day (OR = 2.04; 95% CI: 1.14–3.66 for ⩾20 cigarettes/day). No association emerged for former smokers (OR = 0.98; 95% CI: 0.66–1.45). Alcohol consumption was associated to increased pancreatic cancer risk, but ORs were significant only among heavy drinkers (ORs: 2.03 and 3.42 for 21–34 and ⩾35 drinks/week, respectively). Pancreatic cancer risk was 4.3-fold higher in heavy smokers (⩾20 cigarettes/day) and heavy drinkers (⩾21 drinks/week) in comparison with never smokers who drunk <7 drinks/week, which is compatible with an additive effect of these exposures.

In conclusion, we found that tobacco smoking and alcohol drinking are two independent risk factors for pancreatic cancer which may be responsible for approximately one third of these cancers in our population.

1. Introduction

Pancreatic cancer is a serious medical and public health problem as it is an aggressive, therapy resistant cancer, difficult to diagnose early, and with limited possibilities for preventive actions. Incidence of pancreatic cancer varies across different European countries, but time trends have generally been rising over the past decades in both men and women.[1] In Italy,

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pancreatic cancer is the seventh most frequent cancer-related cause of death among men (4.6%) and the sixth among women (6.6%).[2]

Several studies found a direct association between tobacco smoking and the risk of pancreatic cancer. The risk increases with intensity and duration of tobacco smoking, and remains elevated after adjusting for alcohol consumption and other potential confounding factors.[3] Recently, a meta-analysis of 82 cohort and case-control studies[4] has estimated a 70% excess risk for current smokers in comparison to never smokers; former smokers also reported a non-significant 30% increase in risk. The authors concluded that, assuming a 30% prevalence of smoking, approximately 20% of pancreatic cancer cases can be attributed to tobacco smoking.[4]

The role of alcohol consumption on pancreatic cancer has been recently revised by an international panel of scientists,[5] who concluded that the indication of an association was limited. Indeed, the majority of cohort[6–12] and case-control[13,14] studies reported no significant relationship, and only four investigations found a direct association.[15–17] Recently, a pooled analysis of 14 cohort studies found a 22% increase in risk for drinkers of $\geqslant$30 grams/day of alcohol compared to abstainers.[18] However, this pooled analysis, as most other investigations on this topic, considered only low-to-moderate alcohol consumption whereas the detrimental effect of alcohol, if any, is likely to emerge among heavy drinkers.

To further investigate the association between pancreatic cancer risk and alcohol and tobacco, and to evaluate possible interactions, we conducted a case-control study in northern Italy where both prevalence and intensity of tobacco smoking and alcohol consumption were elevated.

2. Materials and methods

Between January 1991 and December 2008, we conducted a case-control study on pancreatic cancer in the province of Pordenone and in the greater Milan area in northern Italy. Cases were 326 patients between 34 and 80 years of age (median age: 63 years) with incident pancreatic cancer admitted to major general hospitals in the study areas. Histological or cytological confirmation was available for 179 (54.9%) of them, whereas the remaining cases were diagnosed on ultrasound and/or tomography. Histologically confirmed neuroendocrine tumours of the pancreas were excluded from the present study.

For each case, two controls were matched by study centre, sex, and age. The control group included 652 patients (aged 34–80 years; median age: 63 years) who were interviewed between 1991 and 2008. They were admitted for a wide spectrum of acute conditions to the same hospitals where cases had been interviewed. Subjects admitted for malignant neoplasms, conditions related to tobacco smoking or alcohol consumption, or any disorder that might have induced long-term modification of diet were specifically excluded from the control group. Controls were admitted for traumatic orthopaedic disorders (31%), other orthopaedic disorders (31%), acute surgical conditions (28%), and miscellaneous other illnesses, including eye, nose, ear, skin, or dental disorders (10%). All study participants signed an informed consent, according to the recommendations of the Ethical Committees of the study hospitals. Trained interviewers administered a structured questionnaire to cases and controls during their hospital stay, thus keeping refusal below 5%.

The questionnaire collected information on socio-demographic factors, lifestyle habits, diet, problem-oriented medical history, and family history of cancer. Information on smoking included lifetime status (i.e. never, former or current smoker), daily number of cigarettes/cigars and grams of tobacco pipe smoked, age at starting and duration of the habit. In our computations, 1 g of pipe-smoked tobacco corresponded to one cigarette, and one cigar to three cigarettes. Smokers were subjects who had smoked at least one cigarette/day for at least 1 year. Former smokers were defined as smokers who had abstained from tobacco smoking for at least 12 months before interview. The weekly number of drinks for the five most common alcoholic beverages or groups of beverages (i.e. wine, beer, herb liquors, grappa and spirits) was investigated. Taking into account the different ethanol concentration, one drink corresponded to approximately 125 ml of wine, 330 ml of beer and 30 ml of hard liquor (i.e. about 12 g of ethanol). Ages at starting drinking and, for ex-drinkers, at quitting were also recorded. Former drinkers had abstained from any type of drinking for at least 12 months. The validity and reproducibility of questions on self-reported drinking and smoking habits in our study population were satisfactory.[19,20] Study subjects were further asked to report their height and weight 1 year before cancer diagnosis or interview (in controls), weight at different ages, and lifelong highest and lowest weights. Body mass index (BMI) was computed as weight (kg) divided by squared height (m^2).

Odds ratios (OR) and the corresponding 95% confidence intervals (CI) were calculated by means of multiple logistic regression models conditioned on centre, sex, and quinquennia of age, and adjusted for year of interview, education, self-reported history of diabetes mellitus, BMI, drinking and smoking habits, when mentioned.[21] Interaction between tobacco smoking and alcohol consumption was assessed through the synergic index.[22] Percentage attributable risk was computed using the distribution of the risk factors in pancreatic cancer cases and corresponding 95% CIs were obtained.[23]

The dose-response relationship between tobacco smoking and risk of pancreatic cancer was further investigated using cubic logistic regression splines with the appropriate calculation of pointwise confidence intervals.[24] We selected the optimal number of segments by minimising Akaike's Information Criterion.[24]

3. Results

Table 1 shows the distribution of cases and controls according to socio-demographic characteristics. Although cases tended to be more educated than controls, no significant difference was observed.

In comparison with never smokers (Table 2), current smokers were at increased risk for pancreatic cancer (OR = 1.68; 95% CI: 1.13–2.48), the risk increasing with increas-

Table 1 – Distribution of 326 cases of pancreatic cancer and 652 controls, odds ratios (OR) and corresponding 95% confidence intervals (CI)[a] by socio-demographic characteristics, Italy 1991–2008.

	Cases		Controls		OR (95% CI)
	n	(%)	*n*	(%)	
Centre					
Aviano/Pordenone	175	(53.7)	350	(53.7)	
Milan	151	(46.3)	302	(46.3)	
Sex					
Male	174	(53.4)	348	(53.4)	
Female	152	(46.6)	304	(46.6)	
Age (years)					
<50	32	(9.8)	64	(9.8)	
50–59	89	(27.3)	178	(27.3)	
60–69	122	(37.4)	244	(37.4)	
⩾70	83	(25.5)	166	(25.5)	
Education (years)[c]					
<7	166	(51.2)	350	(53.9)	1[b]
7–11	86	(26.5)	192	(29.5)	0.70 (0.49–1.00)
⩾12	72	(22.2)	108	(16.5)	1.14 (0.77–1.70)
χ^2 trend					0.03; $p = 0.86$

[a] Estimates from conditional logistic regression conditioned on centre, sex and age, and adjusted for year of interview.
[b] Reference category.
[c] The sum does not add up to the total because of missing values.

Table 2 – Distribution of 326 cases of pancreatic cancer and 652 controls,[a] ORs and corresponding 95% CIs by smoking habits, Italy 1991–2008.

	Cases		Controls		OR (95% CI)[b]
	n	(%)	*n*	(%)	
Smoking status					
Never	137	(42.2)	328	(50.9)	1[e]
Former	88	(27.1)	189	(29.3)	0.98 (0.66–1.45)
Current	100	(30.8)	127	(19.7)	1.68 (1.13–2.48)
Cigarettes/day					
<20	55	(16.9)	79	(12.3)	1.49 (0.94–2.38)
⩾20	45	(13.8)	48	(7.5)	2.04 (1.14–3.66)
χ^2 trend					6.71; $p<0.01$
Age at start (years)[c,d]					
⩾19	53	(16.3)	64	(9.9)	1.09 (0.55–2.15)
<19	47	(14.5)	63	(9.8)	1.07 (0.50–2.31)
χ^2 trend					0.02; $p = 0.88$
Duration of smoking (years)[c,d]					
<40	52	(16.0)	59	(9.2)	1.28 (0.62–2.64)
⩾40	48	(14.8)	68	(10.6)	0.93 (0.45–1.93)
χ^2 trend					0.05; $p = 0.82$
Time since quitting (years)[d]					
Current smokers	100	(53.2)	127	(40.2)	1[e]
<11	28	(14.9)	60	(19.0)	0.65 (0.36–1.01)
20–11	30	(16.0)	72	(22.8)	0.55 (0.31–0.98)
⩾21	30	(16.0)	57	(18.0)	0.57 (0.31–1.04)
χ^2 trend					5.20; $p=0.02$

[a] Sums may not add up to the total because of missing values.
[b] Estimates from conditional logistic regression conditioned on centre, gender and age, and adjusted for year of interview, education, history of diabetes mellitus, drinking habits and body mass index.
[c] Current smokers only.
[d] Further adjusted for cigarettes/day.
[e] Reference category.

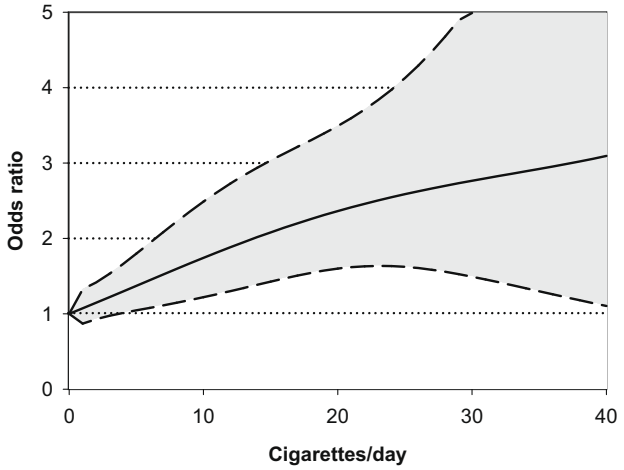

Fig. 1 – Odds ratio (solid line) and 95% confidence intervals (dashed lines) for pancreatic cancer by daily cigarette consumption among current smokers.

ing number of cigarettes/day (OR = 2.04; 95% CI: 1.14–3.66 for ⩾20 cigarettes/day; p-trend < 0.01). The dose-response relationship is compatible with a linear effect (Fig. 1). No significant effects emerged for age at starting and duration of smoking (Table 2). People who had quit smoking showed the same risk of pancreatic cancer as never smokers (OR = 0.98; 95% CI: 0.66–1.45).

Table 3 shows the distribution of cases and controls according to drinking habits. Although not significant, both current and former drinkers were at increased risk for pancreatic cancer (ORs were 1.44; 95% CI: 0.92–2.27 for current and 1.51; 95% CI: 0.79–2.91 for former drinkers). A positive trend emerged for amount of total alcohol (p-trend < 0.01), with significant ORs for higher levels of consumption (2.03 and 3.42 for 21–34 and ⩾35 drinks/week, respectively). The increase in risk for heavy drinkers was confirmed among never smokers (Table 4). Drinking outside meals was not associated to a higher risk than drinking only at meal times. Among former drinkers, the excess of risk disappeared in those who had quit for ⩾8 years. Wine drinking showed the same pattern of risk for overall alcohol intake, whereas beer and spirits were not significantly associated to pancreatic cancer (data not shown).

The interaction between smoking and drinking habits is shown in Table 4. Compared to never smokers who drunk <7 drinks/week, subjects who were heavy smokers (i.e. ⩾20 cigarettes/day) and heavy drinkers (i.e. ⩾21 drinks/week) showed a 4.3-fold increased risk of pancreatic cancer (95% CI: 1.93–9.56), the risk being compatible with an additive effect of the two exposures (Synergic index = 0.88; 95% CI: 0.24–3.23). Former smokers showed the same pattern of risk associated to alcohol drinking as never smokers. In this study population, 32% of cancer cases were attributable to heavy tobacco smoking and heavy alcohol drinking (data not shown).

4. Discussion

In this case-control study of pancreatic cancer, we found a significant positive association with current smoking and current drinking, with a significant dose-response relationship. In this study population, characterised by heavy alcohol consumption and heavy tobacco smoking, approximately one third of pancreatic cancers may be explained by these behaviours.

Other case-control studies found that current smoking and number of cigarettes smoked increased the risk of pancreatic cancer.[3,14,17,25] Moreover, cohort studies have reported findings that are in line with these conclusions.[3,6,7,10,11,26]

Despite the epidemiological evidence which suggests that smoking is a cause of pancreatic cancer, no clear biological mechanism has been demonstrated. There are numerous chemical carcinogens in cigarette smoke that could play a carcinogenic role. Wynder and colleagues[27] proposed that carcinogens absorbed from tobacco smoke may reach the pancreas through the blood, or alternatively, through refluxed bile. Some studies have reported higher and different carcinogen-DNA-adduct levels in the pancreas of smokers compared with non-smokers.[28] Nitrosamines, present at high levels in cigarettes, induce pancreatic cancer in animal models.[29] In addition, tobacco contains many other possible carcinogens, including aromatic amines, polycyclic aromatic hydrocarbons, and metals such as cadmium.[3]

In this study, a significant increased risk was observed with increasing amount of alcohol consumption with an approximately 3-fold higher risk in heavy drinkers as compared to never drinkers. The epidemiological evidence on the association between alcohol consumption and pancreatic cancer risk is weak. Most previous investigations did not find any significant association with alcohol.[6–12,14] However, the association was usually investigated in populations with low-to-moderate alcohol consumption, which may have precluded the possibility of detecting such an effect. Indeed, in our study, the excess risk was appreciable only for a consumption ⩾21 drinks/week and a similar excess risk was found in the few previous studies that included heavy drinkers.[15,17,30]

Heavy alcohol consumption is a well-known major cause of acute and chronic pancreatitis. Chronic pancreatitis has been linked with pancreatic cancer.[31] Furthermore, constant heavy alcohol consumption can interact with other risk factors (i.e. smoking habit), which can ultimately affect the multi-step process of carcinogenesis and lead to the development of pancreatic cancer.[31]

The present work examined the interaction between consumption of alcohol beverages and tobacco smoking. Our results are in agreement with a previous study[32] and confirm an independent effect of cigarette smoking and alcohol consumption with an approximately 5-fold risk for heavy smokers and heavy drinkers. Moreover, the effect of alcohol drinking among former smokers was the same as among never smokers, thus supporting the argument for quitting smoking.

Potential limitations of this study design should be addressed. First, the presence of recall bias is a possibility, as cases may recall their habits differently than controls. However, awareness of any particular smoking and alcohol consumption hypothesis in pancreatic cancer aetiology was limited in the Italian population at the time of the study. Furthermore, the questionnaire was administered to cases and

Table 3 – Distribution of 326 cases of pancreatic cancer and 652 controls[a], ORs and corresponding 95% CIs by drinking habits, Italy 1991–2008.

	Cases		Controls		OR (95% CI)[b]
	n	(%)	*n*	(%)	
Drinking status					
Never	44	(13.5)	102	(15.6)	1[e]
Former	28	(8.6)	54	(8.3)	1.51 (0.79–2.91)
Current	254	(77.9)	496	(76.1)	1.44 (0.92–2.27)
Drinks/week					
<7	46	(14.1)	106	(16.3)	1.04 (0.60–1.80)
7–13	44	(13.5)	89	(13.7)	1.47 (0.83–2.62)
14–20	55	(16.9)	117	(17.9)	1.50 (0.86–2.62)
21–34	52	(16.0)	109	(16.7)	2.03 (1.10–3.74)
⩾35	57	(17.5)	75	(11.5)	3.42 (1.79–6.55)
χ^2 trend					14.93; $p < 0.01$
Age at start (years)[c,d]					
⩾23	74	(22.7)	139	(21.3)	1.22 (0.71–2.09)
19–22	97	(29.8)	170	(26.1)	1.16 (0.68–1.98)
<19	62	(19.0)	172	(26.4)	0.80 (0.46–1.39)
χ^2 trend					1.57; $p = 0.21$
Duration of drinking (years)[c,d]					
<37	80	(24.5)	159	(24.4)	1.07 (0.60–1.88)
37–46	82	(25.2)	166	(25.5)	0.97 (0.55–1.70)
⩾47	71	(21.8)	156	(23.9)	1.15 (0.63–2.09)
χ^2 trend					0.12; $p = 0.73$
Drinking pattern[c,d]					
Only at meals	178	(54.6)	364	(55.8)	1.13 (0.70–1.82)
Also outside meals	65	(19.9)	122	(18.7)	0.96 (0.49–1.86)
Time since quitting (years)[d]					
Current	254	(90.1)	496	(90.5)	1[e]
<8	17	(6.0)	27	(4.9)	1.15 (0.56–2.35)
⩾8	11	(3.9)	25	(4.6)	0.79 (0.35–1.82)
χ^2 trend					0.09; p=0.76

[a] Sums may not add up to the total because of missing values.
[b] Estimates from conditional logistic regression conditioned on centre, sex and age, and adjusted for year of interview, education, history of diabetes mellitus, smoking habits and body mass index.
[c] Current drinkers only.
[d] Further adjusted for drinks/week.
[e] Reference category.

Table 4 – Distribution of pancreatic cancer cases and controls, ORs and corresponding 95% CIs[a] by smoking and drinking habits, Italy 1991–2008.

	Drinking habits (drinks/week)[b]						Total
	<7		7–20		⩾21		
	Ca:Co	OR (95% CI)	Ca:Co	OR (95% CI)	Ca:Co	OR (95% CI)	OR (95% CI)
Smoking habits							
Never	47:133	1[c]	54:119	1.68 (1.00–2.82)	25:53	2.42 (1.20–4.86)	1[c]
Former	19:40	1.09 (0.53–2.21)	19:51	1.52 (0.74–3.12)	41:76	2.67 (1.38–5.17)	1.09 (0.73–1.63)
Current (cigarettes/day)							
<20	12:24	1.65 (0.71–3.85)	17:27	1.76 (0.81–3.82)	22:24	4.15 (1.87–9.18)	1.53 (0.97–2.41)
⩾20	11:8	3.33 (1.08–10.23)	9:8	3.78 (1.15–12.36)	21:27	4.29 (1.93–9.56)	2.38 (1.37–4.15)
Total		1[c]		1.46 (0.98–2.17)		2.53 (1.58–4.07)	

[a] Estimates from conditional logistic regression conditioned on centre, sex and age, and adjusted for year of interview, education, history of diabetes mellitus and body max index.
[b] Former drinkers excluded.
[c] Reference category.

controls by the same interviewers under similar conditions in a hospital setting, thus minimising information bias. Second, the possible presence of selection bias may hinder results. However, cases and controls were enrolled from the same hospital catchment areas and careful attention was paid to exclude from the control group subjects admitted for any condition related to the exposures under study, including tobacco smoking and alcohol drinking. In addition, our findings are strengthened by the nearly complete participation of identified cases and controls.

In conclusion, we found that tobacco smoking status and alcohol drinking are two independent risk factors for pancreatic cancer, which explain approximately one third of cases in this population.

Conflict of interest statement

None declared.

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