Attributable Risks for Pancreatic Cancer in Northern Italy[1]

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Abstract

The proportions of pancreatic cancer cases attributable (or attributable risks) to tobacco smoking, high consumption of meat, low consumption of fruit, family history of pancreatic cancer, and previous history of pancreatitis were computed by using data from a case-control study conducted in Northern Italy. Between 1983 and 1992 a total of 362 incident, histologically confirmed exocrine pancreatic cancer cases and 1408 controls admitted to the same network of hospitals for acute, non-neoplastic, nondigestive, nonhormone-related disorders, were interviewed. The ARs were 14% for tobacco smoking, 14% for high consumption of meat, and 12% for low consumption of fruit. Overall, these factors explained 23% of pancreatic cancer in the population. The proportion of cases attributable to tobacco smoking was greater among males (20%) as compared with females (5%), as well as were the attributable risks for a diet with a high consumption of meat and a low consumption of fruit (25% in males *versus* 18% in females). In conclusion, almost one-fourth of pancreatic cancer cases in this population were explainable in terms of a few identified simple risk factors. Smoking cessation and a healthier eating pattern would prevent approximately 1500 pancreatic cancer deaths in Italy every year. In the absence of effective early detection and therapeutic tools for the disease, the intervention on these factors would, thus, have a relevant impact in reducing pancreatic cancer mortality.

Introduction

Pancreatic cancer is a common form of cancer, with increasing incidence and mortality rates in most developed countries over the last decades and a dismal prognosis (1, 2). The only established risk factor for pancreatic cancer is cigarette smoking (3–7). Among other factors associated with pancreatic cancer, coffee and alcohol consumption have been extensively studied, but neither has been consistently associated (8, 9). Several studies have addressed the issue of diet and pancreas cancer (10–14). In summary, high intakes of selected fats and meat appear to increase risk, and vegetable and fruit consumptions seem to have a protective effect. A medical history of pancreatitis (15, 16) has been associated with subsequent pancreatic cancer risk, whereas an association with diabetes remains open to discussion in terms of causal inference (17, 18). Pancreatic cancer shows some degree of family aggregation (19).

Although a number of studies on determinants for pancreatic cancer have quantified the associations in terms of relative risks, few of them have provided information on the proportion of cases in the population attributable to various risk factors under investigation. This is a function not only of the strength of an association but also of the prevalence of the risk factors in each population (20). Thus, from a public health perspective, primary prevention (*i.e.*, avoiding exposure to known risk factors) appears to be the only way to reduce the burden of the disease, and AR[3] proportions are of considerable interest in order to estimate the number of cases, at least in principle, preventable.

Therefore, with the aim of assessing the role of major identified risk factors on pancreatic cancer, we used data from a case-control study conducted in Northern Italy to estimate the AR percentages, *i.e.*, the proportion of cases in the population attributable to exposure to a few selected risk factors in this population.

Subjects and Methods

The data were derived from an ongoing case-control study based on a network of teaching and general hospitals in the Greater Milan (Italy) area. Recruitment of cases of pancreatic cancer and the corresponding controls began in January 1983; the present analysis is based on data collected before December 1992.

The general design of this investigation has been described previously (19, 21). In summary, trained interviewers identified and questioned cases of pancreatic cancer and controls admitted to the same network of hospitals, using a structured questionnaire, including information on sociodemographic factors, personal characteristics, lifestyle habits (such as smoking, alcohol drinking, and consumption of coffee and other methylxanthine-containing beverages), frequency of consumption of 14 selected indicator foods, and a problem-oriented personal and family medical history. All information was related to the time before the onset of symptoms that led to hospital admission.

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[3] The abbreviations used are: AR, attributable risk; OR, odds ratio; CI, confidence interval.

Cases. The subjects included in the present analysis were 362 (229 males and 133 females) patients <75 years (median age, 60 years) with histologically confirmed incident (*i.e.*, diagnosed within the year before the interview) cancer of the exocrine pancreas. They were admitted to the National Cancer Institute, to several university hospitals, and to the Ospedale Maggiore of Milan, which includes the four largest teaching and general hospitals in Milan, covering almost all diagnostic and treatment oncological facilities in the Greater Milan area.

Controls. The comparison group comprised 1408 subjects (1031 males and 377 females) younger than 75 years (median age, 56 years) admitted for a wide spectrum of acute, nonneoplastic, nondigestive, nonsmoking, nonalcohol-related disorders to the same network of teaching and general hospitals than cases. Thirty-four % had traumatic conditions, 17% nontraumatic orthopedic disorders, 37% acute surgical conditions, and 12% other miscellaneous diseases, such as ear, nose and throat, and skin or dental disorders.

Participation rate was >95% for both cases and controls. All cases and controls were directly interviewed during their hospital stay, and proxy interviews were not accepted.

Data Analysis and Control for Confounding. ORs, as estimators of relative risks of pancreatic cancer, and their 95% CIs were computed using unconditional multiple logistic regression (22). The variables included in the regression equations were sex, age in decennia (except for the first category defined by age <45 years), area of residence (Lombardy, other Northern, Central, and Southern Italy), education (<7, 7–11, and ≥12 years of schooling), risk factors of pancreatic cancer identified in this population: tobacco smoking (never smokers, exsmokers, and current smokers), history of pancreatitis (present/absent), family history of pancreatic cancer in first-degree relatives (present/absent), and weekly frequency of consumption (approximate tertiles based on the distribution of controls) of meat (low, 0–3 servings/week; intermediate, 4–6; and high, ≥7) and fruit (low, 0–6; intermediate, 7; and high, ≥8). Coffee consumption, alcohol intake, and history of diabetes were not related to pancreatic cancer in the present dataset (OR was close to unity and statistically nonsignificant), and subsequently, the ARs for these factors were not computed.

AR proportions were computed by means of the method described by Bruzzi *et al.* (20), which allows their estimation by using data from case-control studies. The method requires the knowledge of the distribution of the exposure to the risk factors only among cases, provided that they are representative of the whole diseased population, and of the OR associated to the exposure. Thus, by using the multivariate OR, population ARs were computed for each separate risk factor and for various combinations of them for all of the subjects and in separate strata of sex and age. For the sake of simplicity, the AR for one factor was based on the assumption of moving all the subjects to the lowest exposure level of the same factor. Because the logistic model assumes a multiplicative effect on the OR, the AR for the combination of two or more factors may not be equal to the sum of the AR for each risk factor because of the correlation among various risk factors. Corresponding variance calculations and 95% CIs of the ARs were obtained as described by Benichou and Gail (23), by means of an *ad hoc*-developed SAS macro.

Results

The distribution of pancreatic cancer cases and controls according to sex, age, level of education, and the other variables considered is shown in Table 1, and the corresponding ORs are presented in Table 2. Ever smokers had an OR of 1.3 of developing pancreatic cancer of borderline statistical significance as compared to never smokers, the risk increasing with increased number of cigarettes smoked and the duration of habit. Pancreatic cancer risk was also associated with a high consumption of meat (OR = 1.3), as well as with a low consumption of fruit (OR = 1.6). Pancreatitis was reported by 6.6% of cases and 1.3% of controls, yielding an OR of 3.4. The risk of pancreatic cancer was also increased among subjects with a first-degree relative affected by the disease (OR = 2.7).

The proportions of cases attributable to the risk factors considered on the basis of the assumption of moving all the subjects to the lowest exposure level are shown in Table 3. Fourteen % of cases were explained by smoking, 14% by a high consumption of meat, and about 12% by a low consumption of fruit. A previous history of pancreatitis explained 5% of cases, whereas the AR for history of pancreatic cancer in a first-degree relative was 2%. Twenty-two % of cases were attributable to simultaneous exposure to the dietary factors considered (high consumption of meat and low consumption of fruit), and 23% were attributable to smoking exposure and low consumption of

Table 1 Distribution of 362 cases of pancreatic cancer and 1408 controls according to sex, age, level of education, and selected risk factors (Milan, Italy, 1983–1992)

	Pancreatic cancer		Controls	
	n	(%)	*n*	(%)
Sex				
Males	229	(63.3)	1031	(73.2)
Females	133	(36.7)	377	(26.8)
Age group (yr)				
<45	24	(6.6)	264	(18.8)
45–54	84	(23.2)	382	(27.1)
55–64	136	(37.6)	459	(32.6)
65–74	118	(32.6)	303	(21.5)
Level of education[a] (yr)				
<7	192	(53.6)	669	(47.8)
7–11	95	(26.6)	414	(29.6)
≥12	71	(19.8)	317	(22.6)
Tobacco smoking				
Never smokers	137	(37.8)	526	(37.4)
Exsmokers	85	(23.5)	295	(21.0)
Current smokers	140	(38.7)	587	(41.7)
Meat intake (frequency of consumption)				
Low	105	(29.0)	440	(31.3)
Intermediate	120	(33.2)	464	(33.0)
High	137	(37.8)	504	(35.8)
Fruit intake (frequency of consumption)				
High	188	(51.9)	764	(54.3)
Intermediate	106	(29.3)	435	(30.9)
Low	68	(18.8)	209	(14.8)
History of pancreatitis				
No	338	(93.4)	1390	(98.7)
Yes	24	(6.6)	18	(1.3)
Family history of pancreatic cancer				
No	348	(96.1)	1393	(98.9)
Yes	14	(3.9)	15	(1.1)

[a] Information is missing for some individuals.

Table 2 OR[a] and 95% CI of pancreatic cancer for the risk factors considered, for all subjects and in separate strata of sex (Milan, Italy, 1983–1992)

	All subjects	Males	Females
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Tobacco smoking			
Never smokers	1[b]	1[b]	1[b]
Exsmokers	1.3 (0.9–1.9)	1.4 (0.9–2.2)	0.9 (0.4–2.0)
Current smokers	1.3 (0.9–1.7)	1.3 (0.9–1.9)	1.3 (0.8–2.2)
Meat intake (frequency of consumption)			
Low	1[b]	1[b]	1[b]
Intermediate	1.2 (0.9–1.6)	1.1 (0.7–1.6)	1.5 (0.9–2.5)
High	1.3(0.9–1.7)	1.3 (0.9–1.9)	1.3 (0.8–2.2)
Fruit intake (frequency of consumption)			
High	1[b]	1[b]	1[b]
Intermediate	1.2 (0.9–1.6)	1.3 (1.0–1.9)	1.0 (0.6–1.6)
Low	1.6 (1.2–2.3)	1.7 (1.1–2.5)	1.6 (0.9–3.0)
Family history of pancreatic cancer			
No	1[b]	1[b]	1[b]
Yes	2.8 (1.2–6.2)	1.8 (0.5–6.1)	4.7 (1.5–15.1)
History of pancreatitis			
No	1[b]	1[b]	1[b]
Yes	3.4 (1.7–6.8)	3.2 (1.3–7.7)	4.4 (1.4–13.5)

[a] Estimates from unconditional logistic regression including terms for sex (if appropriate), age, area of residence, level of education, and the other risk factors in the table.
[b] Reference category.

fruit (Table 3). Tobacco smoking and pancreatitis were responsible for 17% of cases.

The AR to the same risk factors according to separate strata of sex are also presented in Table 3. The proportion of cases attributable to tobacco smoking was greater among males (20% of cases) as compared with females (5%). Similarly, a diet characterized by high consumption of meat and low consumption of fruit was more important among males (25%) than in females (18%), and the difference became larger when tobacco was also considered (38% of male *versus* 12% of female cases). However, none of these differences was significant, and all the CIs largely overlapped.

ORs and the corresponding ARs were also computed separately for subjects below age 60 years or 60 years or older. The only notable differences were the absence of significant association with tobacco smoking among the elderly, whereas the OR was 1.7 in the younger subjects, corresponding to an AR of 30% (95% CI = 10–49%); furthermore, a low consumption of fruit was associated with a greater risk of pancreatic cancer in the elderly (OR = 2.1), accounting for an AR of 22% (95% CI = 9–35%).

Discussion

Almost one-fourth of the cases of pancreatic cancer in this population can be explained by a few selected risk factors, namely tobacco smoking and high intake of meat and low intake of fruit (38% of male and 12% of female cases). Family history of pancreatic cancer, in principle not an avoidable cause, accounted for a 2% of cases.

In terms of relative risk estimation, cigarette smoking has long been reported as the main risk factor for pancreatic cancer, both from cohort and case-control studies (3–7). A dose-response relationship, although weak, has been reported in many studies, as well as a decline in risk after quitting smoking (1, 3, 5, 7). The OR for smoking of 1.3 is consistent with the previous research, also considering the smoking habits of the elderly Italian generations (24). In relation with diet, our data agree with the pattern of increasing risk for high intake of meat and decreasing risk for low consumption of fruit (10, 11).

Scarce information on the proportion of pancreatic cancer cases attributable to tobacco smoking, as well as to other potential risk factors, have been provided. The 1989 Surgeon General reported (5), based on United States mortality statistics, that approximately 30% of pancreatic cancer deaths were attributable to cigarette smoking. Silverman *et al.* (7) estimated from data of a large case-control study conducted in three areas of the United States that elimination of cigarette smoking would prevent 27% of pancreatic cancer cases. Ji *et al.* (25) derived from data collected in a case-control study conducted in China that 24% of pancreatic cancer cases among men and 6% among women could be attributed to cigarette smoking. Our estimates by sex are similar to those reported by Ji *et al.* (25). Although our figure (males and females 14%; upper 95% confidence limit, 28%) is lower than the American estimate (27%), it is in broad agreement with it. However, these differences may be due to the different prevalences of ever smokers among the North American study (69%) and ours (62%) and, particularly, to the low prevalence of smoking among Italian women, reflected by an AR of only 5%, as well as the lower number of cigarettes smoked in Italy as compared to North America, particularly in the past (24, 26). Although our estimate of AR was based on a multivariate OR that was adjusted for a number of potential risk factors, the estimate did not differ when adjustment was only carried out for age and sex as reported in the study by Silverman *et al.* (7) or when the exposure to cigarette smoking was examined in more detail, *i.e.*, the number of cigarettes smoked and the duration of the habit.

For other risk factors considered, to our knowledge no estimation of their AR has been published, except for chronic pancreatitis. Gold and Cameron estimated (27), based on a relative risk of 16 (provided in the study of Lowenfels *et al.*; Ref. 15) and on an incidence of chronic pancreatitis of 3.5–4/100,000, that the population AR of pancreatic cancer would be approximately 0.1%. Our estimate of the AR (5%) is higher and may be influenced by inclusion of acute as well as chronic pancreatitis, as discussed elsewhere (16).

With reference to differences in AR estimates in males and females, the difference observed for tobacco smoking is noteworthy, reflecting the different smoking pattern among males and females. However, this figure may change in the near future because the prevalence of smoking among women in Italy has substantially increased over the last few decades (24). The AR for low fruit consumption was higher in males, probably reflecting a different dietary pattern among males or some bias due to underreporting of fruit consumption. Only inconsistent patterns, moreover, were observed with reference to separate age groups, and none of the differences across various strata of sex and age groups was significant.

Among the potential limitations of this study, there is its hospital-based design, with all of its consequent strengths and limitations (22). However, in this investigation attention was given to excluding patients admitted for diseases related to smoking or alcohol from the control group, as well as to any admission diagnosis known or potentially related to dietary

Table 3 AR[a] percentage and 95% CI of pancreatic cancer for the risk factors considered and for selected combinations, for all subjects and in separate strata of sex (Milan, Italy, 1983–1992)

	All subjects	Males	Females
	AR (95% CI)	AR (95% CI)	AR (95% CI)
Tobacco smoking	13.6 (−1.1–28.3)	19.6 (−3.3–42.6)	5.3 (−8.1–18.8)
Meat consumption	14.2 (−1.8–30.3)	11.5 (−9.6–32.7)	19.7 (−4.6–44.0)
Fruit consumption	12.1 (2.1–22.1)	15.7 (3.3–28.1)	5.9 (−11.4–23.3)
History of pancreatitis	4.7 (1.9–7.5)	3.9 (0.5–7.2)	6.4 (1.3–11.6)
Family history of pancreatic cancer	2.5 (0.3–4.6)	1.0 (−1.1–3.1)	5.3 (0.8–9.9)
Meat consumption plus fruit consumption	22.3 (8.1–36.5)	25.3 (7.2–43.5)	18.0 (−5.1–41.1)
Tobacco smoking plus fruit consumption	22.7 (3.2–42.3)	38.0 (9.6–66.4)	12.4 (−20.7–45.6)
Tobacco smoking plus history of pancreatitis	17.5 (2.8–32.2)	21.1 (−2.0–44.4)	12.6 (−1.2–26.3)

[a] On the assumption of moving all the subjects to the lowest exposure level.

changes, thus reducing the scope for selection bias. Although only histologically confirmed cases were included, thus assuring the homogeneity of the case group, some potential misclassification could be present given the complexity of the certain diagnosis of pancreatic cancer. As pointed out by Lyon *et al.* (28) and Porta *et al.* (29), a number of cytohistologically confirmed cases did not actually originate in the pancreas (29% in the American series and 9% in the Spanish series), and indeed some cases without pathological confirmation could have been, in turn, pancreatic cancer cases. Unfortunately, no appropriate information was collected in the present study to address this issue.

With reference to possible recall bias, it is unlikely that cases and controls reported their consumption of tobacco, meat, fruit, and other foods in a different way because the association with smoking and the protective effect of fruit and vegetables among pancreatic cancer (and other digestive neoplasms) was not widely recognized and was probably unknown to most subjects interviewed. Concerning past episodes of pancreatitis and family history of pancreatic cancer, however, differential misclassification may have induced some overestimation of the risks observed. Cases suffering from pancreatic cancer might, in fact, be more sensitized than noncancer controls toward recalling past episodes of pancreatic diseases as well as pancreatic cancer in relatives.

Finally, the computation of the AR is based on the assumption that the cases are representative of all the cases in the population (20). Although the area under surveillance is not covered by a population cancer registry and the proportion of cases included among all pancreatic cancers is not known, the hospitals included in the present study comprised the majority of diagnostic and therapeutic facilities in the Milan area. There is little reason to suspect that any sort of differential referral may have acted in the inclusion of pancreatic cancer cases in the present investigation.

In conclusion, about one-fourth of pancreatic cancer cases in this population area were explainable in terms of a few identified simple risk factors. Quitting smoking would prevent approximately 1000 pancreatic cancer deaths in Italy every year (of a total of 6700 deaths; Ref. 30), and this figure would increase up to 1500 with the adoption of a healthier eating pattern (*i.e.*, high fruit and vegetable consumption). In the absence of effective early detection and therapeutic tools for this fatal disease, the intervention on these risk factors would, thus, have a relevant impact on reducing pancreatic cancer mortality, currently the fifth leading cause of cancer death in both sexes combined in Italy (30).

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