Attributable Risks for Pancreatic Cancer in Northern Italy

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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 cancers (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 AR3 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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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 oncolgical 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, non-neoplastic, nondigestive, nonsmoking, nonalcohol-related disorders to the same network of teaching and general hospitals than cases. Thirty-four % had traumatic conditions, 17% non-traumatic orthopedic disorders, 57% 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
A single page of a document discussing the risk factors for pancreatic cancer, including tobacco smoking, diet, and family history. The page contains a table showing odds ratios (OR) and 95% confidence intervals (CI) for various risk factors. The discussion section mentions the importance of diet, particularly high meat intake and low consumption of fruit, as well as tobacco smoking and family history of pancreatic cancer. The data is presented in a table format, with ORs and CIs for all subjects, males, and females. The page also includes a discussion on the relative risk estimation and the limitations of the study.
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 cytologist 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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References

Table 3 AR* 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)

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AR (95% CI)</td>
<td>AR (95% CI)</td>
<td>AR (95% CI)</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>13.6 (1.1-28.3)</td>
<td>19.6 (3.3-42.6)</td>
<td>5.3 (1.8-18.8)</td>
</tr>
<tr>
<td>Fruit consumption</td>
<td>14.2 (1-30.3)</td>
<td>11.5 (9.6-32.7)</td>
<td>19.7 (4.6-64.0)</td>
</tr>
<tr>
<td>History of pancreatitis</td>
<td>12.1 (2.1-22.1)</td>
<td>15.7 (3.3-28.1)</td>
<td>5.9 (11.4-23.3)</td>
</tr>
<tr>
<td>Family history of cancer</td>
<td>4.7 (1.9-7.5)</td>
<td>3.9 (0.5-7.2)</td>
<td>6.4 (1.3-11.6)</td>
</tr>
<tr>
<td>Meat consumption</td>
<td>2.5 (0.3-4.6)</td>
<td>1.0 (1-1.3-3.1)</td>
<td>5.3 (0.8-9.9)</td>
</tr>
<tr>
<td>Tobacco smoking plus fruit consumption</td>
<td>22.3 (8.1-36.5)</td>
<td>25.3 (7.2-43.5)</td>
<td>18.0 (5.1-41.1)</td>
</tr>
<tr>
<td>Tobacco smoking plus history of pancreatitis</td>
<td>22.7 (3.2-42.3)</td>
<td>38.0 (9.6-66.4)</td>
<td>12.4 (20.7-45.6)</td>
</tr>
</tbody>
</table>

* On the assumption of moving all the subjects to the lowest exposure level.

| Tobacco smoking plus fruit consumption | 25.3 (7.2-43.5) | 18.0 (5.1-41.1) |
| Tobacco smoking plus history of pancreatitis | 22.7 (3.2-42.3) | 38.0 (9.6-66.4) | 12.4 (20.7-45.6) |

| 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 | 22.7 (3.2-42.3) | 38.0 (9.6-66.4) | 12.4 (20.7-45.6) |

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