Abstract

We questioned 369 patients with histologically proved cancer of the pancreas and 644 control patients about their use of tobacco, alcohol, tea, and coffee. There was a weak positive association between pancreatic cancer and cigarette smoking, but we found no association with use of cigars, pipe tobacco, alcoholic beverages, or tea. A strong association between coffee consumption and pancreatic cancer was evident in both sexes. The association was not affected by controlling for cigarette use. For the sexes combined, there was a significant dose-response relation ($P \sim 0.001$); after adjustment for cigarette smoking, the relative risk associated with drinking up to two cups of coffee per day was 1.6 (95 per cent confidence limits, 1.0 to 3.0), and that with three or more cups per day was 2.7 (1.6 to 4.7).

This association should be evaluated with other data; if it reflects a causal relation between coffee drinking and pancreatic cancer, coffee use might account for a substantial proportion of the cases of this disease in the United States. (N Engl J Med 1981; 304:630-3.)

Over the past few decades, cancer of the pancreas has emerged as one of the most important neoplasias in human beings. It now accounts for approximately 20,000 deaths annually in the United States. Causative factors have been sought in several previous studies, but only cigarette smoking has emerged as a consistent, though relatively weak, exogenous risk factor. We report the results of a study that was planned to reevaluate the relation of this disease to smoking and to examine the role of alcohol consumption as a possible confounding variable. Data were also obtained on intake of tea and coffee—factors that have not been adequately investigated in this disease.

Methods

We conducted a case-control interview study. The cases were patients with histologic diagnoses of cancer of the exocrine pancreas who were in any of 11 large hospitals in the Boston metropolitan area and Rhode Island between October 1974 and August 1979. Patients with tumors of the islet cells, peripancreatic duodenal mucosa, or ampulla of Vater were not included. We identified 578 patients and interviewed 405 of them. Twenty patients died and 35 were discharged before an interview could be arranged; 78 were too sick to be interviewed, 14 had language difficulties, and 26 refused the interview. Also excluded from the analysis were eight nonwhites, five for-...
Alcohol

The relative risk associated with drinking at any time was significant (confidence interval, 1.1 to 1.9). The combined estimate of the risk associated with regular drinking was 0.8 (confidence interval, 0.6 to 1.3, and that of nondrinkers of coffee, but the dose-response relation was flat. Among women, both categories of consumers of three or more cups per day had significantly elevated risks, and the dose-response relation (as measured by the Mantel test) was highly significant (P<0.001). For the sexes combined, with a simultaneous adjustment for sex and age, the trend was also highly significant (chi-square, 11.0), and the adjusted relative risks for consumers of no cups per day, one to two, three to four, and at least five were 1.0, 2.1, 2.8, and 3.2, respectively.

The data on use of cigarettes are shown in Table 1. There was a weak positive association. Although only the data for women showed a significant dose-response relation, the estimate of the relative risk associated with smoking at any time for both sexes combined was 1.4; the difference from the referent risk was significant (confidence interval, 1.1 to 1.9).

Alcohol

Table 2 shows a comparison of use of alcoholic beverages by cases and by controls. No notable or significant association appeared. The combined estimate of relative risk associated with drinking at any time was 0.9, with a confidence interval of 0.6 to 1.3, and that associated with regular drinking was 0.8 (confidence interval, 0.5 to 1.3).

No difference between cases and controls was found in the statements about the type of alcoholic beverage used most frequently (data not shown).

Coffee

An unexpected association of pancreatic cancer with coffee consumption was evident (Table 4). Among men, each category of coffee consumption had a statistically significant excess risk as compared with that of nondrinkers of coffee, but the dose-response relation was flat. Among women, both categories of consumers of three or more cups per day had significantly elevated risks, and the dose-response relation (as measured by the Mantel test) was highly significant (P<0.001). For the sexes combined, with a simultaneous adjustment for sex and age, the trend was also highly significant (chi-square, 11.0), and the adjusted relative risks for consumers of no cups per day, one to two, three to four, and at least five were 1.0, 2.1, 2.8, and 3.2, respectively.

Interaction

Since no association was observed with use of alcoholic drinks, tea, pipe tobacco, or cigars, the principal interaction of interest was that between cigarette use and coffee use. This relation was explored in the analysis presented in Table 5. The data showed a consistent association of pancreatic cancer with coffee drinking within each category of smoking, and the data for all smokers and nonsmokers showed a consistent trend with coffee drinking after adjustment for smoking. With the Mantel extension, the chi-square value for the trend with coffee consumption (after adjustment for smoking as well as age and sex) was 10.6 (P<0.001). The association with smoking within categories of coffee consumption was less clear, and the relative risks for ex-smokers and current smokers, adjusted for coffee consumption, did not differ significantly from unity.


**DISCUSSION**

Our findings with regard to association of cancer of the pancreas with cigarette use and alcohol consumption are consistent with those of previous investigators. The association with cigarette use has been most extensively explored. Weakly positive associations were found in two other case-control studies and in the large cohort studies in British physicians, American veterans, and the American Cancer Society population. The relative risks for cigarette smokers as compared with nonsmokers were 2.3 in the larger case-control study and 1.6, 1.8, and an average of 2.2 in the three cohort studies. These values are comparable to the figure of 1.4 in our study. In one small case-control study, a weak and nonsignificant association was found only in women; among men, there was no difference in cigarette-smoking habits between cases and controls. However, the inclusion of patients with smoking-related diseases among the hospitalized controls in that study would have served to conceal a weak relation. Adjustment for coffee consumption did not entirely remove the association with cigarette smoking in our own data, although the association was not significant after such adjustment. The possible confounding influence of coffee consumption was not evaluated in the other studies.

The relation between alcohol use and pancreatic cancer has been less extensively studied, but a lack of association has been found in one case-control study and in a proportional mortality analysis of a large series of deaths of alcoholics. An association with wine drinking was reported in one study, but the numbers were relatively small, the difference was not conventionally significant, and potential confounding factors were not evaluated. Overall, it seems unlikely that alcohol consumption has any role in the origin of cancer of the pancreas — an observation that is of some interest in the light of the obvious role of this substance in chronic pancreatitis.

In a recently reported case-control study involving 94 patients with pancreatic adenocarcinoma and a similar number of hospital controls, Lin and Kessler noted that the cases tended to drink more decaffeinated coffee than did the controls. In view of the recently observed high association with decaffeinated coffee, it seems unlikely that this particular type of beverage has a causal relation to cases of pancreatic cancer appearing at present. It seems more likely that the high consumption of decaffeinated coffee noted by Lin and Kessler is a reflection of generally high coffee consumption by these patients in the past. These authors gave no data on the use of regular coffee by their subjects.

Although the positive association with coffee consumption that we observed must be evaluated with other data before serious consideration is given to the possibility of a causal relation, it is worth noting that some of the descriptive features of the epidemiology of cancer of the pancreas seem to be consistent with such a relation. The apparent increase in frequency of cancer of the pancreas in recent decades and the low rates observed in Mormons and Seventh-Day Adventists would be compatible with a causative role for either coffee consumption or cigarette smoking. However, the relatively small excess of men with the disease in proportion to women would seem to be more suggestive of a role for coffee rather than for cigarettes. Some 10 years ago, correlating trade statistics in 20 countries with rates of death from cancer, Stocks reported a positive correlation between coffee consumption and rates of pancreatic cancer; the association was present in both sexes, although it was significant only in men. We note also the recent report of the simultaneous occurrence of cancer of the pancreas in a husband and wife who both added “coffee syrup” to ground coffee before percolating it.

Our use of a control group composed of hospitalized patients must be discussed. It is possible that these patients reduced their coffee consumption because of illness and that their replies were affected.
even though the question was related to the time before the onset of their illness. Indeed, Rosenberg et al. reported a lower proportion of coffee consumers among hospitalized women with chronic disease than among women admitted for emergencies. However, the differences noted by Rosenberg et al. between patients with acute and chronic illness were much smaller than those between the cases and controls in our study. Although the majority of control patients in our series had chronic disease, pancreatic cancer itself is a chronic disease, and in theory it would seem as likely as any other disorder to induce a change in coffee consumption. It is a matter for speculation whether such a bias is likely to be greater in our case series or in patients with the diagnoses represented in our control series. It is inconceivable that this bias would account for the total difference between cases and controls, but it is possible that risk may be either overestimated or underestimated on this account. We note, however, that the relative risks shown in Table 4 were similar whether the patients with other cancers or the patients with nonmalignant disorders were used as the control group.

If the association between coffee consumption and pancreatic cancer is confirmed and found to be causal, the relation will have some importance in quantitative terms. Cancer of the pancreas is now the fourth most common fatal malignant disease in the United States. If the distribution of coffee consumption in our control group reflects that in the general population, with relative risks of 1.8 associated with the use of one to two cups daily and 2.7 associated with three or more cups daily, we estimate the proportion of pancreatic cancer that is potentially attributable to coffee consumption to be slightly more than 50 per cent. This estimate emphasizes the need to determine whether the association exists in other data and to evaluate its causal or noncausal nature.

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**REFERENCES**