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# Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma

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**A hospital-based case-control study of pancreatic cancer was conducted in Athens in 1991-92. One hundred and eighty-one patients operated on for cancer of the exocrine pancreas in eight teaching hospitals formed the case series, whereas hospital patient controls and hospital visitor controls formed two independent comparison series. Cases and controls were matched by hospital, gender, and age in a 1:1:1 ratio, and every matched triplet was interviewed in person by the same researcher. Results indicate that tobacco smoking increased the risk of pancreatic cancer, whereas neither coffee drinking nor consumption of alcoholic beverages were associated with the disease. Diabetes mellitus, cholelithiasis, and pancreatitis were associated positively with risk of pancreatic cancer, whereas allergic asthma was inversely (but not significantly) related to the disease. There was a suggestion that earlier age at menarche was associated with increased risk of pancreatic cancer and that parous women were at lower risk. No consistent associations were noted with respect to gastrectomy, other medical conditions or operations, birth order, height, weight, broad occupational groups, or other reproductive variables. The two comparison series were remarkably similar with respect to the whole spectrum of the study variables.**

*Key words*: Case-control study, Greece, pancreatic cancer, risk factors, tobacco smoking.

## Introduction

Cancer of the pancreas is almost always fatal and ranks as the fourth or fifth most common cause of death from cancer in most developed countries.[1] In Greece (1981-85), the age adjusted (World population) mortality from cancer of the pancreas was 5.5 for men and 2.8 for women per 100,000 person-years.[2] As elsewhere in the world,[3] the occurrence of pancreatic cancer in Greece shows an increasing time trend, which is more evident among men (six percent per year from 1960 to 1985) than among women (three percent per year during the same period).[2] A major part of this increase reflects diagnostic improvements and consequences of the preceding and ongoing tobacco epidemic, but other factors also may be involved.[3] The etiology of most cases of pancreatic cancer remains elusive. Several demographic characteristics (including gender, age, and race) have been shown to be risk factors for the disease in different settings,[1] but tobacco smoking[4] represents the

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only established determinant. We have undertaken a case-control study of pancreas cancer in Athens, Greece, using two comparison groups: one including only hospital patients; the other comprised of only healthy hospital visitors. Study variables were socioeconomic, biomedical, reproductive, and nutritional factors, as well as tobacco smoking, coffee intake, and consumption of alcoholic beverages. This paper reports results concerning factors other than nutritional. Findings focusing on dietary variables are presented in another paper in this issue (see pp. 383-9).

## Materials and methods

From January 1991 to September 1992, all residents of the Greater Athens area who were operated on and histologically confirmed for cancer of the exocrine pancreas in eight major teaching hospitals were considered for inclusion in the case-control study. Of these, 181 patients were able and willing to collaborate, while 14 were too sick to be interviewed, and seven refused to participate. Two comparison series were utilized: hospital patient controls, and hospital visitor controls—matched by hospital, gender, and age (± 5 yrs) in a 1:1:1 ratio. Hospital controls were Athens residents hospitalized at the same time at the same hospital for admission diagnosis unrelated to diet and excluding other cancers and gastrointestinal diseases. Of the 181 matched control patients who were approached, only eight refused to participate and these were replaced with another eight appropriately matched patients. Of the hospital controls, 93 (52 percent) had fractures or traumatic injuries; 24 (13 percent) had hernias; 11 (six percent) had appendicitis; 11 (six percent) had ear, nose, and throat conditions; 11 (six percent) had eye diseases (excluding cataract); nine (five percent) had external abscesses; seven (four percent) had other skin conditions; six (three percent) had simple goiter; four (two percent) had varicose veins; and five (three percent) had sciatica. Hospital visitor controls were Athens residents who were visiting patients hospitalized in the same wards as the patients with cancer of the pancreas at the same time. Of the 181 matched visitors who were approached, 13 refused to participate and these were replaced with another 13 appropriately matched visitors. Two experienced visiting nurses conducted the interviews, and every matched triplet was interviewed by the same visiting nurse.

The questionnaire covered demographic, socioeconomic, and reproductive variables, as well as information concerning personal characteristics and medical histories. Consumption of alcoholic beverages, tobacco, and coffee was evaluated by questions probing the type, amount, and duration of consumption over an extended period before the onset of the present disease (for cases) or a comparable period before the interview (for controls).

Conditional logistic regression modeling was utilized[5] through the SAS statistical package,[6] controlling for age, gender, and hospital of origin (as well as for interviewer identity). In some models, additional variables were controlled for, in order to address problems of possible mutual confounding. The following variables were examined:

- medical events or conditions (as genuine risk factors, or as indicators of comparability between cases and the two control series);
- place of residence before the age of 40 years (early environment as indicator of risk or selection bias);
- years of schooling (as indicator of socioeconomic risk gradient or selection bias);
- sibship size and birth order (as proxy variables of early life infection patterns[7]);
- height and weight before the onset of the present disease;
- principal occupation (broad groups);
- coffee drinking (in cups per day, on the average; virtually all coffee drinkers in the age groups under consideration consume Greek coffee);
- tobacco smoking (in cigarettes per day, on the average, before the onset of the present disease—very few were ex-smokers and they were grouped together with current smokers); and
- average consumption of alcoholic beverages (in glasses per day; although the ethanol content of alcoholic beverages varies, the usual serving size is inversely related to ethanol content, so that every glass serving contains approximately the same amount of ethanol[8]).

Linear trend was evaluated by representing a variable as an ordered variable in the modeling.

## Results

The distribution of patients with pancreatic cancer and their age-, gender-, and hospital-matched controls is shown in Table 1. Since matching for age was not exact, the three age distributions were not identical; the differences, however, were neither statistically significant nor substantial. In the subsequent analyses, age ≤ 44 was included in the 40-49 group.

Table 2 presents the frequency of reporting of all medical events or conditions that were mentioned by at least 10 persons in any of the series. The three series were very similar with respect to eight of the 10 medical variables included in the table. The only consistent and statistically significant differences between the case series on the one hand and the two control series on the

**Table 1.** Distribution of 181 persons with pancreas cancer and an equal number of age- (± 5 yrs) and gender-matched controls in two comparison series (hospital and visitor controls)

| | Age (yrs) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≤44 | 45-49 | 50-54 | 55-59 | 60-64 | 65-69 | 70-74 | 75-79 | 80+ | Total |
| Males | | | | | | | | | | |
| Cases | 1 | 13 | 10 | 14 | 9 | 23 | 24 | 11 | 10 | 115 |
| Hospital controls | 1 | 8 | 10 | 18 | 7 | 24 | 21 | 14 | 12 | 115 |
| Visitor controls | 1 | 11 | 11 | 15 | 20 | 24 | 16 | 14 | 3 | 115 |
| Females | | | | | | | | | | |
| Cases | 2 | 1 | 2 | 10 | 12 | 11 | 10 | 15 | 3 | 66 |
| Hospital controls | 2 | 1 | 3 | 5 | 9 | 17 | 12 | 11 | 6 | 66 |
| Visitor controls | 2 | 1 | 6 | 8 | 10 | 13 | 18 | 7 | 1 | 66 |

**Table 2.** Frequency of reporting of specified medical events or conditions by 181 persons with pancreatic cancer and an equal number of age- and gender-matched controls in each of two comparison series

| Event or condition | Pancreas cancer | Hospital controls | Visitor controls | Adjusted rate ratios (95% confidence interval)[a] | |
|---|---|---|---|---|---|
| | | | | Cases *cf* hospital controls | Cases *cf* visitor controls |
| Tonsillectomy | 37 | 27 | 32 | 1.42 (0.84-2.39) | 1.22 (0.70-2.11) |
| Appendectomy | 56 | 63 | 49 | 0.85 (0.56-1.30) | 1.22 (0.76-1.95) |
| Treatment for gastric ulcer | 8 | 8 | 10 | 1.00 (0.38-2.66) | 0.78 (0.29-2.09) |
| Treatment for duodenal ulcer | 17 | 15 | 14 | 1.15 (0.55-2.43) | 1.25 (0.59-2.67) |
| Treatment for gastritis | 14 | 12 | 14 | 1.18 (0.53-2.64) | 1.00 (0.48-2.10) |
| Treatment for hemorrhoids | 34 | 26 | 22 | 1.44 (0.79-2.63) | 1.80 (0.96-3.38) |
| Cholelithiasis | 42 | 18 | 16 | 2.50 (1.40-4.46) | 2.73 (1.51-4.94) |
| Hypertension | 48 | 38 | 46 | 1.35 (0.83-2.18) | 1.06 (0.67-1.67) |
| Diabetes mellitus | 34 | 6 | 8 | 6.60 (2.58-16.91) | 7.50 (2.64-21.29) |
| Long-term medication | 104 | 121 | 106 | 0.67 (0.43-1.03) | 0.95 (0.62-1.47) |

[a] Adjusted for age, gender, and hospital through conditional logistic regression.

other concerned diabetes mellitus (DM) and cholelithiasis, two conditions that may represent genuine risk factors for cancer of the pancreas. The two control series were fairly similar with respect to all 10 variables shown in Table 2.

For nine cases with pancreatic cancer and DM, diabetes was diagnosed at least 10 years before the diagnosis of that cancer, whereas for six controls with DM (all controls combined), diabetes was diagnosed at least 10 years before age at interview. Therefore, DM represents a highly significant risk factor for pancreatic cancer even when a latency of at least 10 years is postulated (baseline was subjects without diabetes; rate ratio 3.6; $P \sim 0.0002$).

With respect to conditions rarely reported, there were no noticeable differences between the three series in the frequency of reporting of adenoidectomy, hepatitis, skin allergies, tuberculosis, and thyroid conditions. Pancreatitis was mentioned by four cases, one hospital control ($P \sim 0.22$) and no visitor control ($P \sim 0.06$), whereas allergic asthma was mentioned by one case, four hospital controls ($P \sim 0.22$), and two visitor controls ($P \sim 0.50$). When the two control series were combined, the relative risk (RR) and the $P$ value were 8.2 and 0.03 for pancreatitis, and 0.33 and 0.28 for allergic asthma.

Table 3 shows univariate frequency distributions of patients with pancreatic cancer and persons in the two control series by several demographic and socioeconomic variables, as well as associated rate ratios. There were no statistically significant, consistent patterns with respect to sibship size, birth order, height, weight before disease onset, and principal occupational group (after controlling for other demographic variables). There was also virtually no association with respect to energy intake ($P > 0.50$). Cases were more likely than controls in either series to have lived the earlier part of their lives in semi-urban and rural areas and they were somewhat better educated. However, these differences may reflect selective hospital-admission patterns,

**Table 3.** Univariate frequency distribution of 181 persons with pancreatic cancer and an equal number of age- and gender-matched controls in each of two comparison series by demographic and socioeconomic variables

| Variables and categories | Pancreas cancer | Hospital controls | Visitor controls | Rate ratios (95% confidence intervals)[a] | |
|---|---|---|---|---|---|
| | | | | *cf* Hospital controls | *cf* Visitor controls |
| Place of residence before age of 40 yrs | | | | | |
| Mainly rural or semi-urban | 78 | 64 | 59 | Baseline | Baseline |
| Mainly Athens or other urban | 103 | 117 | 122 | 0.72 (0.47-1.11) | 0.63 (0.40-0.98) |
| Sibship size | | | | | |
| One | 5 | 12 | 10 | 0.46 (0.15-1.38) | 0.58 (0.19-1.77) |
| Two | 12 | 15 | 16 | 0.86 (0.34-2.22) | 0.80 (0.34-1.89) |
| Three | 42 | 30 | 27 | 1.51 (0.83-2.73) | 1.76 (0.98-3.16) |
| Four | 41 | 31 | 33 | 1.43 (0.79-2.59) | 1.42 (0.82-2.46) |
| Five | 23 | 30 | 28 | 0.74 (0.36-1.51) | 0.93 (0.47-1.84) |
| Six or more | 58 | 63 | 67 | Baseline | Baseline |
| Birth order | | | | | |
| First | 53 | 50 | 49 | Baseline | Baseline |
| Second | 44 | 42 | 36 | 0.97 (0.54-1.73) | 1.11 (0.60-2.08) |
| Third | 32 | 32 | 37 | 0.95 (0.53-1.70) | 0.73 (0.38-1.41) |
| Fourth | 26 | 29 | 21 | 0.81 (0.42-1.57) | 1.19 (0.60-2.34) |
| Fifth | 12 | 9 | 14 | 1.24 (0.49-3.14) | 0.77 (0.32-1.85) |
| Sixth or higher | 14 | 19 | 24 | 0.67 (0.29-1.51) | 0.49 (0.22-1.09) |
| Height in cm | | | | | |
| <160 | 28 | 21 | 27 | Baseline | Baseline |
| 160-164 | 31 | 36 | 32 | 0.58(0.25-1.33) | 0.94 (0.45-1.93) |
| 165-169 | 41 | 55 | 46 | 0.52 (0.23-1.17) | 0.87 (0.39-1.93) |
| 170-174 | 46 | 34 | 41 | 0.95 (0.40-2.24) | 1.09 (0.48-2.51) |
| 175+ | 35 | 35 | 35 | 0.72 (0.29-1.81) | 0.97 (0.40-2.36) |
| Weight in kg before disease onset | | | | | |
| <60 | 15 | 18 | 9 | Baseline | Baseline |
| 60-64 | 18 | 21 | 15 | 1.07 (0.42-2.71) | 0.75 (0.27-2.06) |
| 65-69 | 30 | 14 | 26 | 2.55 (0.98-6.60) | 0.63 (0.23-1.71) |
| 70-74 | 28 | 36 | 31 | 0.88 (0.38-2.06) | 0.53 (0.20-1.36) |
| 75-79 | 27 | 23 | 21 | 1.53 (0.61-3.84) | 0.70 (0.26-1.86) |
| 80-84 | 22 | 23 | 31 | 1.26 (0.52-3.09) | 0.36 (0.13-1.03) |
| 85-89 | 21 | 18 | 23 | 1.45 (0.54-3.91) | 0.47 (0.15-1.44) |
| 90+ | 19 | 28 | 24 | 0.84 (0.34-2.07) | 0.44 (0.16-1.25) |
| Years of schooling | | | | | |
| 0-5 | 47 | 62 | 41 | Baseline | Baseline |
| 6-11 | 84 | 81 | 102 | 1.43 (0.87-2.34) | 0.73 (0.44-1.22) |
| 12+ | 50 | 38 | 38 | 1.80 (1.00-3.24) | 1.17 (0.63-2.17) |
| Principal occupation | | | | | |
| Rural | 40 | 33 | 28 | 1.92 (1.01-3.65) | 1.89 (0.99-3.58) |
| Labor (urban) | 38 | 57 | 53 | Baseline | Baseline |
| Employee | 30 | 32 | 30 | 1.40 (0.72-2.73) | 1.43 (0.70-2.90) |
| Professional | 8 | 7 | 9 | 1.66 (0.55-4.96) | 1.33 (0.47-3.82) |
| Commerce | 26 | 20 | 17 | 1.78 (0.89-3.54) | 2.22 (1.02-4.87) |
| At home (women) | 39 | 32 | 44 | 2.30 (1.02-5.17) | 1.14 (0.58-2.21) |

[a] Adjusted for age, gender, and hospital through conditional logistic regression.

rather than a genuine risk profile of pancreatic cancer and they were controlled for in the subsequent analysis (although their confounding influences were minimal).

Table 4 examines the relation of tobacco smoking, coffee drinking, and consumption of alcoholic beverages to the risk of pancreatic cancer after controlling for age, gender, hospital of origin, past residence, years of schooling, and DM (cholelithiasis did not noticeably confound these associations). There was no evidence that consumption of either coffee or alcoholic beverages was associated with increased risk of pancreatic cancer in this dataset. Tobacco smoking was related positively to risk of pancreas cancer, although the association was more evident in the comparison with visitor controls and reached statistical significance only when a linear trend was evaluated.

In Table 5, reproductive variables were examined among women patients and controls. There was some

**Table 4.** Univariate frequency distribution of 181 persons with pancreas cancer and an equal number of age- and gender-matched controls in each of two comparison series by tobacco smoking, coffee drinking, and consumption of alcoholic beverages

| | Pancreas cancer | Hospital controls | Visitor controls | Rate ratios (95% confidence intervals)[a] | |
|---|---|---|---|---|---|
| | | | | *cf* Hospital controls | *cf* Visitor controls |
| Coffee drinking (cups per day) | | | | | |
| 0-1 | 32 | 26 | 26 | Baseline[a] | Baseline[a] |
| 1-2 | 42 | 43 | 37 | 0.80 (0.41-1.57) | 0.90 (0.46-1.74) |
| 2-3 | 69 | 69 | 73 | 0.84 (0.47-1.52) | 0.73 (0.38-1.38) |
| 3-4 | 17 | 23 | 19 | 0.59 (0.26-1.36) | 0.65 (0.27-1.58) |
| 4+ | 21 | 20 | 26 | 0.85 (0.38-1.93) | 0.58 (0.24-1.37) |
| | | | | incremental per 1 cup/day[b] | |
| | | | | 0.89 (0.73-1.09) | 0.85 (0.68-1.05) |
| Alcoholic beverages (glasses per day) | | | | | |
| 0 | 61 | 63 | 59 | Baseline[a] | Baseline[a] |
| <1 | 43 | 28 | 43 | 1.53 (0.82-2.86) | 0.94 (0.52-1.72) |
| 1-2 | 24 | 22 | 21 | 1.06 (0.53-2.13) | 1.09 (0.52-2.26) |
| 3-4 | 7 | 12 | 10 | 0.58 (0.20-1.72) | 0.62 (0.20-1.91) |
| 4+ | 28 | 39 | 31 | 0.68 (0.34-1.34) | 0.81 (0.39-1.68) |
| | | | | incremental per 1 glass/day[b] | |
| | | | | 0.89 (0.77-1.02) | 0.96 (0.83-1.11) |
| Tobacco smoking (cigarettes per day) | | | | | |
| Nonsmoker | 73 | 84 | 87 | Baseline[a] | Baseline[a] |
| 1-10 | 15 | 15 | 20 | 1.25 (0.54-2.88) | 1.01 (0.45-2.28) |
| 11-20 | 45 | 37 | 33 | 1.52 (0.85-2.74) | 1.89 (1.02-3.50) |
| 21+ | 48 | 45 | 41 | 1.36 (0.76-2.44) | 1.84 (0.93-3.63) |
| | | | | incremental per 10 cigarettes/day[b] | |
| | | | | 1.05 (0.85-1.28) | 1.32 (1.04-1.67) |

[a] Controlling through conditional logistic regression for age, gender, and hospital.
[b] Controlling through conditional logistic regression for age, gender, hospital, past residence, years of schooling, and diabetes mellitus.

evidence that nulliparity, early age at menarche, and late age at menopause may be risk factors for pancreatic cancer, although the respective associations were not statistically significant in comparison with either control series. There were no clear patterns with respect to other reproductive variables (age at first birth, number of miscarriages, or induced abortions—data not shown).

## Discussion

The present study has the strengths and weaknesses of hospital-based case-control investigations. On the positive side, response rates were very high, and all interviews were conducted in person, in a medical setting, under strictly comparable conditions, and with little or no time pressure. On the negative side, hospital-based case-control studies are thought frequently to be inferior to population-based, retrospective investigations because of the likelihood of selection bias. However, for diseases with poor prognoses, like cancer of the pancreas, most population-based case-control studies must rely on proxy interviews for a large proportion of cases. Moreover, response rates among eligible population controls are typically low, and this can introduce substantial selection bias of unpredictable direction. In another context, many case-control studies, whether hospital- or population-based, are susceptible to information bias and therefore inferior to cohort studies that do not face this problem. It should be noted, however, that cohort studies rely on self-administered questionnaires, whereas in case-control studies, exposure assessment frequently is based on extensive interviewer-administered questionnaires that can improve precision and allow better control of confounding. In the present study, the use of two control groups and the generation of essentially similar results in comparison of cases to either control group, increases the confidence on the validity of the findings.

Tobacco smoking is an established component cause of cancer of the exocrine pancreas. Earlier studies,[4] more recent investigations,[9-16] a previous small study in Greece,[17] and the present investigation, indicate that regular tobacco smoking of about one pack of cigarettes per day increases the risk for pancreatic cancer to about twice the corresponding risk among nonsmokers. In this study, the association was less clear and statistically nonsignificant in comparison with hospital controls, possibly because tobacco smokers are slightly over-represented even among patients hospi-

**Table 5.** Univariate frequency distribution of 66 women with pancreas cancer and an equal number of age matched controls in each of two comparison series by reproductive variables

| Variables and categories | Pancreas cancer | Hospital controls | Visitor controls | Rate ratios (95% confidence intervals)[a] | |
|---|---|---|---|---|---|
| | | | | *cf* Hospital controls | *cf* Visitor controls |
| Age at menarche in years | | | | | |
| < 13 | 21 | 17 | 21 | 1.00 — | 1.00 — |
| 13 | 27 | 24 | 22 | 0.74 (0.27-2.04) | 1.06 (0.41-2.76) |
| 14 + | 18 | 25 | 23 | 0.48 (0.16-1.43) | 0.55 (0.18-1.66) |
| Menopausal status | | | | | |
| Premenopausal | 2 | 2 | 3 | — | — |
| Age at menopause | | | | | |
| < 45 | 10 | 15 | 11 | 1.00 — | 1.00 — |
| 45-49 | 23 | 17 | 17 | 1.85 (0.48-7.16) | 1.32 (0.41-4.25) |
| 50 + | 31 | 32 | 35 | 1.50 (0.46-4.89) | 1.22 (0.40-3.71) |
| Parity | | | | | |
| Nulliparous | 12 | 13 | 4 | 1.00 — | 1.00 — |
| Parous | 54 | 53 | 62 | 0.62 (0.18-2.16) | 0.39 (0.11-1.40) |

[a] Controlling through conditional logistic regression for age, hospital, past residence, years of schooling, cigarette smoking, diabetes mellitus, as well as mutually (age at menarche, parity, menopausal status, and age at menopause).

talized for conditions currently considered as unrelated to tobacco smoking. The results of the present study were also compatible with the existing substantial evidence that ethanol intake is apparently unrelated to risk of pancreatic cancer.[8,13,14,18,19]

A working group convened in 1990 by the International Agency for Research on Cancer (IARC) to evaluate the carcinogenic risk to humans by (among others) coffee intake, concluded that "taken as whole, the data are suggestive of a weak relationship between high levels of coffee consumption and the occurrence of pancreatic cancer, but the possibility that this is due to bias or confounding is tenable."[20] Since then, several case-control studies have examined the association. In some of them, statistically significant positive associations were noted,[16,18] but in the majority[9,11,13,14,19,21] (including a series of studies undertaken in the context of the SEARCH project of IARC[14,19,21] and the present investigation) there was either no association or a non-significant inverse association. It appears that the collective evidence is tilting towards the null hypothesis. However, the wide publicity that accompanied an early report linking coffee drinking to pancreatic cancer[22] makes case-control studies particularly vulnerable to information bias of unknown direction and magnitude. The problem is compounded by proxy-interviewing in many studies and by possible selection bias in population-based case-control studies with high nonparticipation rates among eligible controls.[14,19,21] It seems unlikely that coffee drinking is a strong determinant of risk for pancreatic cancer, but the existence of a weak positive association cannot be excluded. This issue will be resolved conclusively only when results of several ongoing large cohort studies become available. It may be noted, in this context, that in a large cohort study in Japan, daily coffee drinkers had a significantly higher risk for cancer of the pancreas than non-daily consumers[12] (reported rates, per 100,000 person-years, 78.4 and 14.5, respectively).

It has been reported that height may be a risk factor for pancreatic cancer, whereas weight, or weight adjusted for height, may not.[23,24] It also has been suggested that cases of cancer of the pancreas may have increased energy intake which is not reflected in increased weight or body mass index (weight/height$^2$), because of differences in energy homeostasis.[23,25,26] No association was evident in the present study between height, weight, or energy intake and cancer of the pancreas. It seems more likely that, in case-control studies, the reported increase of energy intake among patients with pancreatic cancer reflects more complete dietary ascertainment for cases than for controls[27] rather than an adverse effect of physical activity on pancreas cancer risk, or unspecified changes in thermogenesis in persons developing pancreatic cancer.[23] In the present study, as in a previous one,[24] female cases tended to have earlier age at menarche than female controls, and there was a suggestion that parity may convey some protection. These associations must be examined in other studies before biomedical mechanisms are proposed to explain them.

DM is widely considered to be a risk factor for pancreatic cancer,[3,10,13,19] although findings of no association also have been reported.[28] It has been assumed frequently that the association reflects islet cell destruction by direct extension of the tumor. This view

has been challenged by the fact that, in many cases of pancreatic cancer, DM is diagnosed many years before the appearance of cancer (for a critical assessment of the existing evidence, see review by Boyle *et al*[3]). The results of the present study indicate that DM is a significant and important risk factor for pancreatic cancer even after the passage of 10 or more years after the diagnosis of diabetes. It may be that subtle pathologic changes in the early stages of exocrine pancreas carcinogenesis involve or affect the functional integrity of endocrine pancreas, or that both diseases share an etiologic or pathogenetic component.

Pancreatitis was a significant and important risk factor for pancreatic cancer when the two control series were combined in our analyses. Similar results have been reported previously,[13,28] although pancreatitis is not accepted universally as a genuine risk factor for pancreatic cancer.[29] Cholelithiasis (with or without cholecystectomy) was also a risk factor for pancreatic cancer in this study, as well as in some earlier ones.[10] An association of gallbladder pathology with risk of pancreatic cancer would be compatible with hypotheses invoking cholecystokinin in the pathogenesis of this cancer.[30]

In this study, as in several others, no association was found between peptic ulcer (with or without gastrectomy) and risk of pancreatic cancer. By contrast, the findings of the present study are compatible with several reports[19,28,31] suggesting that allergic conditions may indicate reduced risk for cancer of the pancreas. If this inverse association were established conclusively, it would allow an unusual insight on the processes that link immune responses to carcinogenesis.

We found no evidence that birth order (a proxy variable for age at first exposure to several infectious agents[7]) or broad occupational categories were risk factors for pancreatic cancer (the apparent excess risk of rural occupations was accounted for by other demographic variables, notably place of residence before the age of 40 years). However, broad categorization of occupation does not allow identification of particular high-risk occupations, and birth order is not always a sensitive indicator of age-related patterns of exposure to infections.

In conclusion, this study provides evidence that tobacco smoking, pancreatitis, and cholelithiasis increase the risk of pancreatic cancer; that in a fraction of cases, DM may be related intimately to early stages of pancreas carcinogenesis; and that allergic conditions, late menarche, and parity may be associated inversely with risk of pancreatic cancer. The results of this study are compatible with hypotheses postulating that somatometric variables, broad occupational categories, gastrectomy, birth order, and intake of alcoholic beverages or coffee are unrelated to risk for cancer of the exocrine pancreas.

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