

Special topic by C. Dervenis

Epidemiology and risk factors for exocrine pancreatic cancer

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INTRODUCTION

Compared to other gastrointestinal malignancies, exocrine pancreatic cancer is a fairly common malignancy, outnumbered only by colorectal and stomach cancer in the gastrointestinal tract. However, periampullary cancers comprise a mixture of pancreatic and non-pancreatic, "ampullary" or "periampullary" cancers. Each of these has a different biology, leading to somewhat different symptoms and therefore different resectability rates, with ductal adenocarcinoma having the lowest. The focus of this review is ductal adenocarcinoma of the pancreas, which account for 80-90 percent of pancreatic cancers,¹ but together with its less common variants (i.e. mucinous noncystic carcinoma, signet-ring cell carcinoma, adenosquamous carcinoma and undifferentiated carcinoma) it comprises 90-95 percent of all primary pancreatic neoplasias.²

Clinically and scientifically it is important to differentiate also between pancreatic adenocarcinomas and other periampullary tumors (neuroendocrine tumours, cancers of the intrapancreatic bile duct, papilla Vateri and juxtapaillary duodenum) as these non-pancreatic tumors have a much better prognosis, including a potential high cure rate.^{3,4} As an example of this, in a prospective series 1992-1998 the median survivals after pancreatoduodenectomy for carcinoma of the pancreatic head (n=108), distal bile duct (n=32), and papilla of Vater (n=64) were respectively 16, 25, and 24 months.⁵ There are also other, more unusual pancreatic adenocarcinomas, such as cystadenocarcinoma, that must be differen-

tiated from the common pancreatic ductal adenocarcinomas as their biology, though malignant, is distinct.

Also, the ductal adenocarcinomas of the pancreatic body and tail (25-30 percent of all cases) have probably the same biological properties as those of the head of the pancreas. However, due to their surroundings they give rise to pain, jaundice and other symptoms at a later stage, which means that they as a group are more advanced compared the caput cancers.⁶⁻⁸ Therefore, in all presentations of clinical results a line must be drawn between cancers to the right and to the left of the portal vein (or, to be more exact, the dividing line should be drawn at the left border of the portal and superior mesenteric veins).

METHODOLOGICAL PROBLEMS IN EPIDEMIOLOGICAL STUDIES OF PANCREATIC CANCER

Epidemiologic studies on exocrine pancreatic cancer show a large heterogeneity in diagnostic criteria applied to define the cases. Reanalyses conducted after review of diagnostic information have often yielded substantial different results than those based on the first, more crude classifications of disease. Therefore, in good epidemiologic studies of pancreatic cancer, it is warranted that a panel of experts centrally reviews all the existing diagnostic evidence of all patients, regardless of whether they have cytohistological confirmation or not and ir-respectively of their hospital discharge diagnosis.⁹

The death rate of pancreatic cancer is almost the same as its incidence, as the survival over-all is less than 1 percent.¹⁰ In malignant tumors of the pancreas, adenocarcinoma arising from ductal epithelium is most common,

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probably representing at least 90 percent of all cases. There are also present cystadenocarcinomas, malignant islet cell tumors and more uncommon malignancies but these are almost always in epidemiological investigations include under the heading of "pancreatic cancers". This means that there should be allowed up to 10 percent miscalculations regarding the absolute numbers of "ductal pancreatic cancer" when studies are based on registries. However, there are no reasons to believe that this proportion is not relative steady over time, which means that as long as trends are more important than absolute figures, this uncertainty is of minor importance.

Another problem is that reliable cancer statistics in the Western world have been produced not until the 1960s, and in the rest of the world most often even later. Moreover, concerning pancreatic cancer it is only in recent decades that clinicians have been able to diagnose the disease with a reasonable accuracy without laparotomy. Some of the apparent increase in the incidence of pancreatic cancer during 1960-1990 can therefore be explained by more accurate diagnostic methods. For example, comparing the clinical diagnosis of pancreatic cancer in Japan with the diagnosis by autopsy, underdiagnosis was found in 60 percent and overdiagnosis in 33 percent of cases in 1958-1962,¹¹ but in 1982-1983, underdiagnosis was found in only 30 percent and overdiagnosis in only 9 percent of cases.¹² Therefore some part of an increase in incidences may simply represent a higher degree of diagnostic certainty rather than a real increase of number of cases.

Moreover, there has been a change of policy due to better anesthesiology, better economics, changes in ethical considerations etc to palliate also elderly people with abdominal malignancies. This means that old people with pancreatic cancer have a higher degree of probability to get a verification of their cancer of pancreatic cancer today. Fifty years ago many of those patients probably got the diagnosis of "unspecified generalised abdominal malignancy" or "metastatic disease of the liver" instead of a more exact diagnosis. This may also lead to an increase in the reported incidence of pancreatic cancer, even though there has been no real increase.

Nevertheless, increased diagnostic accuracy is unlikely to explain all of the long-standing increase in this tumor observed in many countries. The reason for the steady increase for many years is, however, mostly unknown. As discussed below, pancreatic cancer is strongly related to smoking. Some of the temporal changes in the incidence of this tumor are undoubtedly caused by changes in smoking pattern, but based on an carcino-

genic thinking the increases in pancreatic cancer ought to follow an increases in tobacco smoking not until about a 20-year lag period.

INCIDENCE

It is often reported that pancreatic cancer is responsible for about 5 percent of all cancer-related deaths in the Western world,¹³⁻¹⁶ and ranks fifth in cancer incidence and mortality worldwide.¹⁷⁻¹⁹ The important conclusions of these type of incidence figures are, however, that it should be remembered that pancreatic cancer is one of the most common cancer types in the human, and – unfortunately and so far – the frequency figures for the appearance and for the deaths in pancreatic cancer are almost equal. This means that if the incidence is not rising the cured patients should be looked upon as exceptions to a grim prognosis rather than a usual outcome after radical surgery.

In an over-viewing perspective the age-adjusted incidence of pancreatic ductal adenocarcinoma in developed countries range between 8 and 12/100 000 for males and between 4.5 and 7.0/100 000 for females. Incidence rates from most developing countries range between 1.0 and 2.5/100 000.²

As with other digestive tract tumors, the risk of pancreatic cancer increases rapidly with age: only approximately 20 percent of these cancers are seen before age 60 and pancreatic cancer must be understood as a disease primary of the elderly. It is extremely rare in individuals under 35 years of age and uncommon under 45 years. The age-specific incidence rate for pancreatic cancer shows a constant increase with age in both males and females in most cancer registries.^{20,21}

In Sweden cancer of the pancreas in 1991 represented 2.4 percent of all male and 2.8 percent of all female cancers.²² The Swedish National Cancer Registry, to which it is mandatory by law to report all new cases of cancer in Sweden, registered 35 383 cases of exocrine pancreatic cancer between 1958 and 1991. The percentage of histologically verified cases (including cytology and autopsy) was 80 percent for both men and women for the whole period, but 84 percent for men and 82 percent for women during the last 14 years. Since 1975 the cases first found at autopsy have been separately recorded, being 20 percent during the first ten years, thereafter going down to around 14 percent, a drop from around 240 to 150 cases a year. The total number of new cases of exocrine pancreatic cancer increased for both sexes until the beginning of the 80s to a total of around 1250 cas-

es a year, whereas the number of new cases among persons under the age of 50 has remained unchanged, about 40 cases a year (all verified by histopathology). When analysing the trends an increasing crude incidence rate was found for men until the beginning of the 70s on 16 per 100 000 and for women until the mid 80s on 15 per 100 000. Regarding the age standardized rates (according to a WHO world population standard) the incidence increased until the beginning of the 70s to 8.5 per 100 000 for men and 6 per 100 000 for women. Thereafter both incidences rates remain at a steady-state until 1988 when there was a change to a clearly decreasing incidence for both men and women, both with regard to crude rates, 11 and 10 per 100 000 men and women, respectively, and age-standardized rates, 5.5 and 4.5, respectively. The reason for this decrease is unknown, and can not be explained by different ways of reporting, autopsy frequency etc, but most probably reflects a genuine reduction of the disease in the Swedish community.

When discussing changing incidences age and gender must be taken in account. In a study 1961-1990 where 75 percent of cases were based on autopsy 651 men and 663 women were studied in southern Sweden no change in incidence over time was observed for men. In older and middle-aged women there was, however, a statistically significant increase. The average relative change in women above age 64 was 1.7 percent per year after age-adjustment and in women aged 55-64 years 2.6 percent per year.²³

For a long time it has been repeatedly quoted in the text-books that the incidence of pancreatic cancer has been increasing in the Western world²⁴ and the rise has been documented to in most countries with cancer registries of good quality during the 60s, 70s and 80s.^{25,26} In many European countries, except Sweden and the United Kingdom, also the mortality rate for pancreatic cancer is documented to increase for both males and females.¹⁶ However, the increasing trend has lately been brooken in Europe, at least for men as their incidence has stabilized or is decreasing. Exceptions regarding this is - so far - Czechoslovakia, Germany, Italy, France, and Spain.^{27,28} However, so far the decreasing trend for pancreatic cancer, as now shown in cancer registry with recently analysed data and published from Denmark, Sweden, France and Iceland^{29,30} is more exceptions than the rule. However, also in some states in the United States the incidence and mortality rates in males have recently declined.^{22,31} On the other hand, the lower incidence for exocrine pancreatic cancer in women is still not uncommonly often increasing, or leveling off. On the other hand

it is according to some registries decreasing, which probably depends on what level the incidence figures start from, possible because more and more females have become smokers in many countries. It has been suggested that the current 25 percent male excess of pancreatic cancer – a difference most obvious in younger men - will disappear in the decades ahead due to this changing pattern.²¹ For exemple, in a US community-based study, the age-adjusted incidence per 100 000 person-years in women increased from 4.5 for the years 1940-1949 to 7.9 for the years 1980-1988. The incidence in men rose from 9.2 in 1940-1949 to 12.8 in 1960-1969 but has remained stable since then.²⁶ Partly, changes in incidence can be hidden by different trends in different cohorts. As an exemple of this, the death rate from pancreatic cancer in the elderly US population increased significantly between 1979 and 1995 in contrast to a trend towards decreasing mortality in the younger age groups.³²

In Japan the age-adjusted mortality rate (adjusted to the 1985 model population) for pancreatic cancer has increased by approximately ninefold in both males (from 1.4 to 12.5 per 100000 populations) and females (from 0.8 to 6.8) during the relatively short time period between 1950 and 1995. However, the rise has begun to level off in both genders since 1985. As in Sweden, the older age group showed the most steep increasing gradient in both age-specific mortality and incidence rates in both sexes, whereas little or no apparent increase was observed in younger age groups. Diagnostic improvement and increased cigarette consumption were believed to be the two major factors contributing to the increased mortality in Japan.³³

The mortality rate for pancreatic cancer is high in Denmark, Sweden, Finland, Ireland, and some other European countries, but is low in Asian and southern European countries. However, the geographic variation is less than with other common gastrointestinal cancers.³⁴ A positive correlation has been observed between geographical latitude and the mortality.³⁵ The age-adjusted death rates for pancreatic cancer in Thailand, Hong Kong and Brazil have been low. In Japan, Hungary and Yugoslavia the rates were intermediate and in the majority of Western countries, e.g. Sweden, UK and USA have had high incidences.²¹ From an international point of view, the rates are generally still higher in Western and industrialized countries than others, although the Maories in New Zealand and Hawaiians in Hawaii also have an exceptionally high incidence.²⁵ As shown above, in Japan the death rate has increased about 14 times - from 0.3 to 4.2/100,000 - since 1935 and is there in the middle

80s the fifth leading cause of death from cancer in Japanese males and the seventh in females. Improvements at the diagnostic quality may account for a part of this marked increase, but most probably not all.²⁵ In France, the risk increased from one generation to another proportionally with an increase of the death rate by 48 percent for men and 27 percent for women between 1955 and 1969³⁶ followed 1970 to 1980 by a death rate increase of 98 percent for men and 61 percent for women.³⁷

In Inuits from Greenland and Canada, with a high consumption of alcohol and tobacco, there was no increased incidence of pancreatic cancer, which indicates that the etiology is multifactorial.³⁸

GENDER DIFFERENCES

Pancreatic cancer has in the literature been described as a predominantly male disease.²⁵ The male to female ratios of mortality range from 1.0 in Thailand to 2.3 in Norway.²¹ Those of incidence ranged from 1.4 in Brazil to 2.9 in France.²⁵ The ratios of US white decrease after age 50, whereas Japanese ratios slightly increase with age.³⁹ There are studies reporting a sex ratio also between cancers of the body and tail to cancers of the head from 2.9/1 to 1/1.8.⁴⁰

Taken together, it seems as exocrine pancreatic cancer is significantly more common in younger men than in younger women, but in higher ages the age-adjusted rates are equal for men and women. The male to female cancer ratio in most countries lies between 1.25 and 1.75 to 1, but the ratio decreases with increasing age. In Sweden, this ratio is 1.75:1 below the age of 50 years and decreases with age so that there is no significant difference after the age of 70 years.^{14,41} A similar observation has been made in most other countries with a high incidence of pancreatic cancer.⁴² Moreover, prior oophorectomy appeared in one study to be significantly more common in women with pancreatic cancer than in controls.⁴³

IMPORTANCE OF ASSESSMENT OF RISK FACTORS

Early diagnosis of cancer has been thwarted because population at risk for developing pancreatic cancer has not been identified until recently. Today there are several known or suggested - on a scientific basis - etiologies of pancreatic cancer, but even though the issue has been extensively studied according to the literature, there is less known about important risk factors in pancreatic cancers than in most other gastrointestinal malignancies.

Moreover, the etiology of cancer of the pancreas seems to be multifactorial, which makes the studies more difficult to interpret.⁴⁴ The demonstrated changes in the incidence of pancreatic cancer are compatible with the hypothesis that lifestyle related factors are involved in the causation of the disease. The contribution of smoking is convincing, as is chronic pancreatitis and some rare genetic diseases, whereas all other risk factors are less well-defined or of limited importance. However, the methodological limitations of most of the epidemiological studies on risk factors for pancreatic cancer, particularly the descriptive and case-control studies, are such that causal interference's regarding these empirical associations currently are not warranted.⁴⁵

Despite this, it is not unimportant to discuss the risk factors in pancreatic cancers in order to find ways for prevention or early diagnosis of the disease. Especially, if there will be better methods for diagnosing pancreatic cancer (e.g. advanced ultrasonography, MRI, CT, and molecular biology based tumor markers) the demography and epidemiological studies in order to define high-risk population may become very important for early diagnosis and treatment.

SOCIO-ECONOMIC STATUS

Pancreatic cancer showed no association with socio-economic status in one large register study, whereas large socio-economic differences in the incidence of stomach cancer for both men and women and a less clear pattern for colorectal cancer were found in the same investigation, with women in more advantaged social groups experiencing higher incidence of colorectal cancers whereas for men there was no significant association.⁴⁶

On the other hand, in a study in Florida the county-specific incidence rates for pancreatic cancer ranged from 0.8 to 8.1 per 100000 per year and were significantly correlated with income ($r=0.35$), cigarette smoking ($r=0.39$), and solid waste ($r=0.47$), the last one attributable to yard trash (grass clippings, and tree and shrub trimmings ($r=0.42$)). The latter finding might, however, probably more indicate that insecticides and herbicides may be responsible for the increased risk than the socio-economic status manifested in the housing standard and geographically location.⁴⁷

Increased risk of pancreatic cancer was also reported among high socioeconomic populations in England and Wales, but a reverse relationship was suggested in the US.^{48,49} However, in general there are no consistent relationships between socioeconomic status and pancre-

atic cancer if the smoking habits are taken in account.

URBAN-RURAL DIFFERENCES

Generally, urban residents have in most studies a slightly higher incidence of pancreatic cancer than rural residents.^{20,21} If there is found a difference, the cancer rates are always higher in urban than rural populations. This has been documented for example in Minnesota, USA,⁵⁰ and in Vaud, Switzerland,²¹ where the incidence rate of pancreatic cancer at least in urban men is higher than in rural men.⁵⁰ This association suggests that environmental factors, such as occupation, dietary habits, etc, of urban residents are different from those of rural residents. However, the rapid equalization between living conditions in urban and rural areas in the Western world makes these differences less predominant. If the difference is still meaningful in Europe,^{51,52} this is probably no longer the case in the US.^{50,52}

RACIAL DIFFERENCES AND MIGRANT STUDIES

Cancer rates are consistently higher in black than in white populations in the US. Age-adjusted incidence rates from pancreatic cancer in blacks are about 1.5-2 times higher than those in whites;^{25,52} the rates being 43 percent higher for black men and 48 percent higher for black women. The pancreatic cancer death rate is lower for male American Indians (69 percent of the rate for Caucasians) but higher for American Indian women (equal the rate for Caucasians). However, this rate is still lower than that for black women.⁵²

US Japanese have had a higher rate of pancreatic cancer than Japanese in Japan,⁵³ but more recently male Japanese in Japan have just as high - or even higher! - incidence rate compared to US Japanese. Among Japanese in the US, the mortality for migrants from Japan was higher than that of US-born children of immigrants.⁵³

Other high-risk populations are the Hawaiians and the Maoris of New Zealand.^{25,54} These ethnic groups present a larger risk than that of the Caucasians living on these two islands. The hypothesis proposing a genetic factor is intriguing because these populations are also at high risk for diabetes.⁵⁵

COFFEE

In 1981, a much cited report suggested that coffee was a strong risk factor for pancreatic cancer.⁵⁶ There

was criticism against that study because the control group included a high proportion of patients with gastrointestinal diseases who might have stopped or reduced their coffee consumption on that account. However, additional analysis showed consistent association when the control group was limited to nongastrointestinal and nonmalignant disorders,^{56,57} but a second report from the same group and almost all subsequent reports have concluded that the evidence is insufficient to establish coffee drinking as a risk factor for pancreatic cancer.⁵⁸⁻⁶² Both positive results,^{63,64} negative ones⁶⁵⁻⁶⁷ and even intermediate ones,⁶⁸ have, however, later been published. A confounding factor may be that there is a strong link between coffee drinking and smoking.

There are still some confusion on this issue, which has not been made less by recent large register studies. In a prospective cohort study of 33976 postmenopausal women in Iowa followed from 1986 to 1994 there was an increased age-adjusted relative risk of pancreatic cancer with coffee intake also after adjustment for smoking status and pack-years of smoking. There was a statistically significant two-fold (95% confidence interval 1.1-4.3) risk of pancreatic cancer for those who drank more than 18 cups of coffee per week, compared to those who consumed less than 7 cups per week. Among never-smokers, the relative risk across coffee intake categories were still positive but were attenuated somewhat.⁶⁹

On the other hand, in a recent Canadian study⁷⁰ of 583 histologically confirmed pancreatic cancer cases and 4813 controls coffee drinking was not related to risk of pancreatic cancer. However, in a case-control study from Spain it was found that patients with pancreatic cancer without activating mutations in the K-ras gene (n=27) had drunk significantly less coffee than cases with a mutation (n=94), with a significant dose-response: the less they drank, the less likely their tumors were to harbor a mutation. So it seems that in pancreatic cancer the K-ras gene may be activated less often among non-regular coffee drinkers than among regular drinkers.⁷¹

In yet another study, there was a higher percentage of drinkers of decaffeinated coffee among the pancreatic cancer cases.⁴³ These data suggest that, if there is a real association between pancreatic cancer and coffee, it is unlikely to be due only to the caffeine constituents of coffee.⁷²

Taken together, although coffee twenty years ago was suspected to be linked to pancreatic cancer,⁵⁶ most recent studies have failed to find any significant relationship between coffee consumption and pancreatic can-

cer^{59,73} and it is most commonly believed by epidemiologists to be no association at all.

TEA

In a prospective cohort study of 33976 postmenopausal women in Iowa followed from 1986 to 1994 there was no association between tea intake and pancreatic cancer.⁶⁹ Also in another study there was no increased risk associated with consumption of teas.⁵⁶ If there is an causal association between tea (e.g. the Western variant) it must be weak, and probably there is no association at all.

There are on the other hand reports of green tea (e.g. the Chinese variant) reducing human cancer risk. In a case control study with 451 patients with pancreatic cancer in Shanghai, China, the odds ratios for pancreatic cancer in men, compared with non-regular tea drinkers, was 0.63 and 0.53 for women.⁷⁴ These interesting data should be explored further, before giving it too much attention.

OTHER DIETARY FACTORS

Several studies have attempted to find particular dietary items that might increase or decrease the risk of pancreatic cancer. Ecological data demonstrate most often a relationship between fat and oil intake and pancreatic cancer,^{75,76} but there is also a positive correlation to the consumption of sugar and protein.⁷⁷ In a recent case-control study, fat intake was related to pancreatic cancer, but there was no association between protein intake and pancreatic cancer.⁷⁷ Overall, fairly consistent patterns of positive associations with the intake of meat, carbohydrates, and dietary cholesterol have been observed. Consistent inverse relationships with fruit and vegetable intakes and, in particular, with two markers of such foods, namely fiber and vitamin C, have also been noted.⁴⁵

Also, excess intake of high energy intake, together with high intake of fat and protein, has been linked to pancreatic cancer in a few studies whereas consumption of fresh fruits and vegetables may be protective.⁷⁸⁻⁸³ In a study of 34000 California Seventh-day Adventists who do not smoke cigarettes or drink alcohol higher consumption of all fruit, dried fruit and legumes was associated with a lower risk of pancreatic cancer.⁸⁴ In other, prospective studies of Seventh-Day Adventists, a low mortality from pancreatic cancer has been found.^{85,86} This is probably due to the compiled effects of abstinence from smoking and drinking alcoholic beverages and coffee and

maybe because most individuals in this population avoid eating meat with concomitant increase in vegetable intake. Mormons, also being less likely to smoke and drink coffee, tea and alcoholic beverages and use fats in cooking, showed a low mortality^{87,88} and incidence of pancreatic cancer^{89,90} further strengthening the bond between the peroral intake and the risk of pancreatic cancer.

A case-control study in Japan showed a statistically significant increased risk with high intake of meat and low intake of green and yellow vegetables for males.^{91,92} The increasing frequency of pancreatic cancer among Japanese people living in the US as compared to those living in Japan could thus be partially explained by a change in their dietary habits.³⁶

There has been shown a positive dose-response relation between Body Mass Index and pancreatic in China.⁹³ Also, in a recent case-control study in Georgia, Michigan, and New Jersey 1986-1989 of 436 persons with pancreatic cancer and 2203 general-population control subjects aged 30-79 years obesity was associated with a statistically significant 50-60 percent increased risk that was consistent by gender and race. Although the magnitude of risk associated with obesity was identical in blacks and whites, a higher percentage of blacks were obese than were whites (women: 38 versus 16%; men: 27 versus 22%). The increased risk was also associated with increasing caloric intake, with subjects in the highest quartile of caloric intake experiencing a 70 percent higher risk than those in the lowest quartile. Subjects in the highest quartile of body mass index had a statistically significant 180 percent higher risk than those in the lowest quartile.⁹⁴

The role of the conversion of cholesterol to cholesterol epoxide as an etiological factor has been raised.⁹⁵ Moreover, non-genotoxic diet factors as unsaturated fat and trypsin inhibitors have been discussed as they in rat models induce putative preneoplastic acinar cell foci.⁹⁶ In a case-control study in Italy (362 cases and 1502 controls) the score for oil (mainly olive oil) intake was inversely related to the risk of pancreatic cancer. The multivariate odds ratios were 0.8 for the intermediate, and 0.6 for the highest score of intake, and the trend in risk was significant.⁹⁷ Other epidemiological studies in several Mediterranean populations have demonstrated that increased dietary intake of olive oil is associated with a small decreased risk, or no increased risk, of pancreatic cancer, despite a high overall lipid intake.⁹⁸

GASTRIC SURGERY AND UPPER GI-ULCERS

Some studies have shown a link between peptic ulcer

disease and pancreatic cancer.^{99,100} The most plausible explanation for this finding is that both diseases are linked to a shared risk factor: smoking.

This is also demonstrated in a Swedish study. It is well recognized that subtotal gastrectomy with a Billroth II-reconstruction increases the risk of a cancer in the gastric remnant in a time-dependent manner. However, whereas the standardized morbidity ratio for gastric carcinoma increased to 4.5 after Billroth II (but not Billroth I) resection after at least 22 years follow-up, the standardized morbidity rate for pancreatic cancer (and pulmonary carcinoma) was not increased and the deaths was evenly distributed over time, which indicates that there is no casual relationship.¹⁰¹ Therefore, there is today enough evidence to state that neither peptic ulcer disease or stomach resections increases the risk for pancreatic cancer.

Further, in a recent US case-control study of 484 cases and 2299 controls subjects with a history of duodenal or gastric ulcer had little or no elevated risk, and those treated by gastrectomy had the same risk as those not receiving surgery.¹⁰²

GALLSTONE DISEASE

Cholelithiasis was early considered to be related to pancreatic cancer,¹⁰³ and one case-control study in Japan showed that a past history of gallstones increased the risk of pancreatic cancer (relative risk 2.5).¹² A cohort study in elderly also found an increased risk of pancreatic cancer associated with a history of cholecystectomy.¹⁰⁴ There was also found a connection in a Swedish population-based cohort of 62615 patients who had undergone cholecystectomy and were followed up for 23 years. After excluding the first year after operation, there were 261 pancreatic cancers versus 217 expected, i.e. a standardized incidence ratio of 1.2 (95% confidence interval 1.1-1.4), and 11 other periampullar cancers versus 7 expected (0.8-2.7). The increased risk of pancreatic cancer was most prominent up to four years after operation, but was also significantly increased 15 years or more after operation.¹⁰⁵

In a recent US case-control study of 484 cases and 2299 controls cholecystectomy appeared to be a risk factor for pancreatic cancer, as well as a consequence of the malignancy. Subjects with a cholecystectomy at least 22 years prior to the diagnosis of pancreatic cancer experienced a 70 percent increased risk, which was marginally significant^{†102} in an US register study of 3.4 million military veterans 1981-1993 the ratio of comorbid

occurrence in choledocholithiasis with pancreatic cancer was 4.3 (95% confidence interval 3.8-4.9).¹⁰⁶

Gallstone-induced acute pancreatitis is the most common cause of acute pancreatitis, but neither gallstones nor cholecystectomy appears to alter the risk of pancreatic cancer in more recent studies.¹⁰⁷ The reason for the earlier found associations may be that initial symptoms of pancreatic cancer may mimic biliary tract disease, explaining why some studies have observed an association between onset of biliary tract disease and cholecystectomy and pancreatic cancer. It must be remembered that gallstones are very common in these age groups - up to 60 percent of persons over 70 years of age¹⁰⁸ - making a concomitant but unrelated association possible. This connection is further strengthened by a comparative study of 100 consecutive cases of pancreatic cancer and 140 age- and gender-matched control subjects. In this study 37 percent of the cancer patients had gallstones which is significant more than the 18 percent in the control group.¹⁰⁹

DIABETES

Pancreatic cancer represent 5-22 percent of all cancers occurring in diabetes. However, diabetes afflicts approximately 5 percent of all adults, and diabetes often accompanies pancreatic cancer. Moreover, pancreatic cancer happens to give rise to diabetes during the course of the disease, which means that there is a considerable risk of overestimation of the true premalignant frequency of diabetes in pancreatic cancer patients.

There are some earlier reports of a causal association between diabetes and pancreatic cancer. However, although a statistical association is present in most epidemiological studies since diabetes can be an early symptom in the development of pancreatic cancer¹¹⁰ this doesn't mean that a causal relationship between diabetes and pancreatic cancer is present. In one prospective study a statistically significant excess of death from pancreatic cancer in diabetics of both genders were found.¹¹¹ In a case-control study, a significant relationship with early-onset diabetes was demonstrated.³⁹ Reports that look closely at the duration of diabetes suggest that although many patients with pancreatic cancer do have diabetes, the diabetes is usually of recent onset and probably secondary to ductal obstruction from pancreatic cancer. Preexisting diabetes of long duration is not likely to lead to an increased risk of pancreatic cancer.^{110,112,113} A cohort study in elderly found an increased risk of pancreatic cancer associated with a history of diabetes.¹⁰⁴ In

a larger study diabetes has been shown to be of limited importance though, and is probably a concomitant factor rather than a causative factor in most cases.

In a recent US case-control study of 484 cases and 2299 controls there were, however, support for diabetes as a risk factor for pancreatic cancer, as well as a possible complication of the tumor. A significant positive trend in risk with increasing years prior to diagnosis of pancreatic cancer was apparent, with diabetics diagnosed at least 10 years prior to diagnosis having a significant 50 percent increased risk. Those treated with insulin had risks similar to those not treated with insulin (odds ratio 1.6 and 1.5, respectively).¹⁰²

In a 12 years of follow-up, 2953 deaths from pancreatic cancer were observed in a cohort of 1089586 men and women who were cancer-free at study entry in 1982. A history of diabetes was significantly related to pancreatic cancer mortality in both men (rate ratio 1.5; 95 % confidence interval 1.3-1.8) and women (1.5; 1.2-1.9). The death rate from pancreatic cancer was twice as high in diabetics as in non-diabetics during the second and third years of follow-up (2.1; 1.6-2.7) but only about 40 percent higher in years 9-12 (1.4; 1.1-1.8).¹¹⁴

In two Danish cohorts of diabetics (n=1659+1499) pancreatic cancer occurred in excess both immediately (<1 year), and during 1-9 years after onset of pancreatic cancer. In yet another Danish study discharge records of 109581 individuals hospitalized with a diagnosis of diabetes from 1977 through 1989 were linked with the national cancer registry records through 1993. For both sexes combined, the standardized incidence ratio for pancreatic cancer was 2.1 (95% confidence interval 1.9-2.4), with a follow-up time of 1-4 years; the ratio declined to 1.3 (1.1-1.6) after 5-9 years of follow-up.¹¹⁵

In a study of six human pancreatic cancer cell lines insulin receptors were demonstrated on all six cell lines and dose dependent increases in cell proliferation were demonstrated in response to insulin. This is of certain interest as patients with type-II diabetics hyper secrete insulin.¹¹⁶

There may also be a correlation between IAPP (islet amyloid polypeptide) and diabetes, with a correlation to diabetes.¹¹⁷

Taken together, the relation of diabetes and pancreatic cancer is one of the most difficult to analyse in pancreatic cancer epidemiology. There is doubtless a positive statistical correlation between the two, but if diabetes is a causative factor or not is less certain. However,

from an empirical and clinical point of view, such a connection is – if present – is weak, and it is more probable that pancreatic cancer causes diabetes or that a third factor causes both pancreatic cancer and diabetes than that diabetes causes pancreatic cancer. Finally, if there after all should be a positive relation between the two, it is most probably only related to diabetes type II. Diabetes type I might even be a protective factor for pancreatic cancer.

CIGARETTE SMOKING AND AROMATIC AMINES

Today there are strong epidemiological evidence that underscores the importance of smoking as a causal agent for experimental as well as human pancreatic cancer.^{58,99,118-126} The risk increase with the number of cigarettes smoked and years of exposure.^{121,127} Follow-up studies of large groups of normal individuals provide the strongest evidence linking smoking and pancreatic cancer. An early cohort study of 50 000 college graduates showed that smoking 10 or more cigarettes per day, as recorded on college health records, resulted in a 2.4-fold increased risk of pancreatic cancer after an interval of 15 or more years.¹²⁸ A study of 34 000 British physicians showed an overall risk in those who smoked 25 cigarettes or more per day three times greater than that for nonsmokers, and there was a clear dose-response.¹²⁷ The dose-response relationship between the risk of pancreatic cancer and the number of cigarettes smoked per day was found also in most of the other of these studies.^{12,39,92,124,125,127} Most studies report that smoking is found to be an independent risk factor, increasing the risk as much as two-fold,⁴⁴ compared with nonsmokers. Altogether, smoking is believed to be the most common cause for pancreatic cancer and is the etiology factor in approximately 30 percent of all cases.

Cigarette smoking is a consistently increased risk factor for pancreatic cancer in all recent epidemiologic studies done, but its role as a carcinogen for pancreatic cancer is weaker than for lung cancer. Despite this, it may be estimated that at least a large number of pancreatic cancer can be prevented if smoking is stopped completely.¹²⁹ If the percentage of smokers remains unchanged, 627000 and 588000 newly diagnosed pancreatic cancer cases among males and females respectively will be expected in the European Union up to 2222 according to a computer simulation.¹³⁰ Theoretically, if all smokers would give up smoking instantly, this number can be reduced by 133000 cases among men and 43000 cases among women. It has been advocated that smoking can

partly explained why there in some countries⁷³ is a tendency to decreasing incidences for pancreatic cancer in men, whereas the femal rate still is increasing. In a recent Canadian study⁷⁰ of 583 histologically confirmed pancreatic cancer cases and 4813 controls the male subjects with 35 or more cigarette pack-years had an increased risk of developing pancreatic cancer relative to never smokers (OR=1., 95% CI 1.0-2.1), whereas women reporting at least 23 cigarette pack-years of smoking had an odds ratio of 1.8 (95% CI 1.3-2.7). In a hospital-based study of 484 male and femal patients with pancreatic cancer and 954 control subjects the odds ratio, compared to never smokers, was 1.6 (95% confidence interval 1.1-2.4) for men and 2.3 (1.4-3.5) for women. In women, but not in men, there was a trend in the odds ratios with years of daily cigarette consumption, but filter cigarettes offered no protection advantage compared to non-filter cigarettes. Among men, the odd ratio was 2.1 (1.2-3.8) for pipe and cigar smokers and 3.6 (1.0-12.8) for tobacco chewers.¹³¹

In a prospective study of 118339 women aged 30-55 years and 49428 men aged 40-75 years who were without a diagnosed cancer were followed-up during 2116229 persons-years pancreatic cancer was diagnosed in 186 individuals. The multivariate relative risk of pancreatic cancer for current smokers was 2.5 (95% confidence intervall 1.7-3.6). A significant, positive trend in risk with increasing pack-years of smoking was onserved, but this association was confined to cigarette consumption within the past 15 years. Compared with participants who continued to smoke, former smokers had a 48 percent reduction in pancreatic cancer risk within 2 years of quitting. Ultimately, the relative risk of pancreatic cancer among former smokers approached that for never smokers after less than 10 years of smoking cessation. Overall, the proportion of pancreatic cancers attributable to cigarette smoking was 25 percent.¹³²

Based on the epidemiological data of association between cigarette smoking and pancreatic cancer, a hypothesis, i.e. the bile containing carcinogens originating from cigarettes causes pancreatic cancer on reflux into the pancreatic duct, was presented.³⁹ In animals a tobacco-specific nitrosamine contained in cigarette smoke produces experimental cancer in two organs: the lung and the pancreas.¹³³ In humans, there is a strong international correlation between pancreatic cancer and lung cancer, suggesting that these two lethal tumors share the same risk factor.³¹ Since the pancreas is exposed only indirectly to inhaled tobacco smoke, the effects of smoking are less pronounced on the pancreas than on the lung.

In a study of lifetime occupational, smoking, and alcohol-consumption histories were collected by means of a self-administered questionnaire from 15463 male cancer patients aged 22 years and over in British Columbia. Except for pancreatic cancer, a significant relationship was found for all cancer sites known to be strongly associated with cigarette smoking.¹³⁴

In a prospective cohort study of 33976 postmenopausal women in Iowa followed from 1986 to 1994 there was an increased age-adjusted relative risk of pancreatic cancer with a dose-response association with smoking. Those with fewer than 22 pack-years and those with 22 or more pack-years of smoking were 1.1 (95% confidence interval 0.5-2.5) and 1.9 (1.1-2.3) times more likely, respectively, to develop pancreatic cancer than were nonsmokers. Current smokers were twice as likely as were nonsmokers to develop pancreatic cancer.⁷⁵

Many enviromental factors that are associated with increased risk for pancreatic cancer may be related to exposure to aromatic amines. At least 30 aromatic amines are present in cigarette smoke,¹³⁵ including 2-naphthylamine and 4-aminobiphenyl, which are proven carcinogens for human bladder cancer. Similarly, the association between meat and fish consumption and the risk of pancreatic cancer, reported by many investigators,^{85,99,136} may be associated with the carcinogenic and mutagenic heterocyclic aromatic amines present in cooked meat and fish (formed during cooking as pyrolysis products of amino acids and proteins).^{78,108,109} In a study of the ability of pancreatic tissues from organ donors to metabolize aromatic amines and other carcinogens it was strong indices that aromatic amines and nitroaromatic hydrocarbons may be involved in the etiology of pancreatic cancer.¹³⁷

Occupations with greater risk of pancreatic cancer, such as chemistry, petrochemical work, hairdressing, and rubber work,^{138,139} may be associated with increased exposure to aromatic amines. However, even though there has been earlier reports on increased incidences of pancreatic cancer, they are almost all single reports and follow-up studies are missing and, moreover, recently reports are not present which might mean that even if there has been an increased risk this is not the case today. On the other hand, there has been discussions if ingestion of fruits and vegetables may confer protection against development of pancreatic cancer. Some components of plats (dithiolthiones and limonene) may induce glutathione transferase and increase levels of glutathione, which may inhibit mutagenic activation of heterocyclic amines.^{140,141} Together, these data suggest an association

– even though clinically of limited importance - between exposure to aromatic amines and pancreatic cancer.

When age, gender, and alcohol consumption was taken into account in a study 1980-1990 the risk of a Ki-ras-mutated tumor was detected in patients who only smoked, but less so in patients who smoked and drank.¹⁴²

Taken together, it is obvious that there is a strong association between smoking and pancreatic cancer. However, it must be understood that all of the changes in incidence of pancreatic cancer cannot be due to smoking. For example, the striking increase in pancreatic cancer mortality in the blacks over age 75 compared to whites in the US contrasts with lung cancer mortality in this age group and suggest causative factors other than cigarette smoking as the cause of this trend.³²

ALCOHOL

Heavy alcohol consumption damages the pancreas, often producing acute and chronic pancreatitis. Some early reports and even case-control studies suggested that there might be a link between alcohol and pancreatic cancer.^{14,43,75,118} However, no association of this kind was reported in other retrospective studies.^{75,143,144} Moreover, no correlation was established in a case-control study by standardizing for smoking¹⁴⁵ and two large follow-up studies of alcoholics showed no association between the two.^{8,146} All recent reports have concluded that alcohol is not a risk factor for pancreatic cancer.^{59,147,148} This was also the conclusion in a recent Canadian study⁷⁰ of 583 histologically confirmed pancreatic cancer cases and 4813 where total alcohol, wine, liquor and beer consumption was not associated with pancreatic cancer.

In the prospective cohort study of the 33976 postmenopausal women in Iowa followed from 1986 to 1994 there was, however, an increased age-adjusted relative risk of pancreatic cancer with the amount of alcohol after adjustment for age, smoking status, and pack-years of smoking. Relative risks of pancreatic cancer according to alcoholic beverage intake were as strong among never-smokers as they were in the total cohort.⁶⁹

In a study 1980-1990 the risk of a Ki-ras-mutated tumor was three times higher in alcohol drinkers than in non-drinkers, and a linear trend was apparent,¹⁴² making it important to take alcohol, coffee and smoking into account when discussing Ki-ras mutation frequency – but also in the evaluation of the way that different risk factors can influence the pancreatic carcinogenicity.

These inconsistent results suggest that even if there is an association between alcohol intake and pancreatic cancer alcoholic beverages play only a small role in the genesis of pancreatic cancer and this may be well explained by an association between alcohol and chronic pancreatitis.

CHRONIC PANCREATITIS

The association between chronic pancreatitis and ductal adenocarcinoma of the pancreas was first discussed some 22-30 years ago,^{149,150} and has been discussed frequently since.¹⁵¹⁻¹⁵⁴ The two conditions not infrequently coexist. It is well recognized that obstruction of the main pancreatic duct in pancreatic cancer leads to fibrosis retrograde to the obstruction. Moreover, a rim of unspecific inflammation is most often found around pancreatic cancers, making for example a negative (regarding cancer cells) fine needle aspiration cytology from a pancreatic tumor of doubtful value.

Though a number of morphologic studies failed to identify lesions that could be considered precursors of pancreatic cancer,^{155,156} more recent epidemiological studies in large cohorts of patients have revealed that chronic pancreatitis definitely is a risk factor for the development of pancreatic cancer. A cohort study of more than 2200 patients in six countries with well-defined chronic pancreatitis revealed a significantly elevated risk of pancreatic cancer: patients with chronic pancreatitis followed-up for two years or more had a 16-fold increased risk of pancreatic cancer; patients with a minimum follow-up period of five years or more had a 14-fold increased risk. Similar risks were found in males and females, and in both alcoholic and idiopathic forms of pancreatitis. The cumulative 25-year risk of pancreatic cancer in patients with any form of chronic pancreatitis was 4 percent.¹⁵⁷ This relative risk in patients compares with 4 in a US Veterans Administration hospital population¹⁵⁸ and nearly 8 in a Swedish study including both patients with acute and chronic pancreatitis.¹⁵⁹ Actually, there are today two studies from Sweden that show a statistically significant correlation between chronic pancreatitis and pancreatic cancer.^{159,160} Additional recent studies have confirmed these findings, so it appears that chronic pancreatitis is a real risk factor for pancreatic cancer.^{158,161-163}

In a case-control study of 142 cases and 307 controls from various American hospitals, four cases and no controls reported a history of pancreatitis,²⁴ but in three of the four cases the onset of pancreatitis was concurrent with diagnosis of pancreatic cancer. A larger study of 490

case-control pairs from California, gave a relative risk of 5 (five cases versus one in the control group).⁹⁹ In an Italian study Fernandez et al¹⁶⁴ compared the relationship between family history of 362 patients with pancreatic cancer and 1408 controls admitted to hospital for non-neoplastic disorders and found that approximately 3 per cent of newly diagnosed pancreatic cancer could be related to a familial component, not dependent on allowance for tobacco, alcohol, dietary factors or a history of pancreatitis. In this report there was also a review of altogether nine cases-control studies giving 65 cases of pancreatitis among 2234 cases of pancreatic cancer patients, which is to be compared to 37 pancreatitis cases among 4039 controls.

In an Italian study 715 cases of chronic pancreatitis were followed-up for a median of 10 years. During that period 61 neoplasms developed, 14 of which were pancreatic cancers. Even when excluding from the analysis the four cases of pancreatic cancer that occurred within 4 years of clinical onset of chronic pancreatitis, the standardized incidence ratio was 13.3 (95% confidence interval 6.4-24.5). The authors concluded that the risk of pancreatic and nonpancreatic cancers are increased in the course of chronic pancreatitis, the former being significantly higher than the latter. The very high incidence of pancreatic cancer in smokers suggest that, in addition to cigarette smoking, some other factor linked to chronic inflammation of the pancreas may be responsible for the increased risk.¹⁶⁵

However, the analysis of a possible connection between chronic pancreatitis and pancreatic cancer is confounded due to large differences in study designs. A review of the possible association was recently published.¹⁶⁶ In a collected series of 16 different studies published 1960-1989 of the prevalence of pancreatic carcinoma in patients with chronic pancreatitis Niderau et al found¹⁶⁷ 86 patients with cancer among 2429 with pancreatitis, giving a prevalence of 3.5 per cent. Beger and coworkers¹⁶⁸ found pancreatic cancer in 6 percent of 504 patients operated on for chronic pancreatitis during a median follow-up time of 14 years. The increased risk relates to all types of chronic pancreatitis and in particular to hereditary pancreatitis.¹⁶⁹ However, since pancreatitis is an uncommon disease, only a small fraction of all pancreatic cancers are causally related to chronic pancreatitis making the overall contribution of chronic pancreatitis to the pancreatic cancer population small - only 5-6 percent of patients with ductal adenocarcinoma seem to develop the tumor on a background of chronic pancreatitis.

Chronic pancreatitis is in most countries due to prolonged excessive drinking and causes a substantial increased risk of pancreatic cancer. The strongest evidence for the association is, however, in (familial) hereditary pancreatitis, first described in 1952.¹⁴⁹ This is a rare familial form of pancreatitis, now considered to be an autosomal dominant trait with incomplete penetrance.¹⁷⁰⁻¹⁷³ This unusual form of chronic pancreatitis is of special interest as the afflicted patients have an increased risk of pancreatic cancer: the estimated cumulative risk of pancreatic cancer to age 70 is 40 percent.⁸⁶ Up to one-third of affected family members develop cancer,¹⁷⁴ but in a large review¹⁷⁵ of 304 patients the incidence of pancreatic cancer was 5 per cent, but the estimated cumulative risk for developing pancreatic cancer in patients with a paternal pattern of inheritance is higher - approximately 75 percent.¹⁶⁹ It may be of pathophysiological interest that the risk also appears to extend to family members who do not have chronic pancreatitis.¹⁷⁴ Because two gene mutations for hereditary pancreatitis have been identified,^{176,177} it is now possible to screen families to determine who is at risk for pancreatic cancer and to plan a rational screening program.

It is still not settled if it is a chronic inflammatory process or the specific pancreatitis that create the increased risk - or if both ways of tumorigenesis are working simultaneously or if it is distinct in different types of patients (i.e. hereditary pancreatitis versus alcoholic pancreatitis). Continuous epithelial regeneration and proliferation are thought to promote carcinogenesis in many organs, but it seems as if hyperplastic or metaplastic ductal changes and K-ras mutations do not inevitably lead to the development of ductal adenocarcinoma.

In a study¹⁷⁸ of resected patients with chronic pancreatitis, i. e. in the selected population where an operation was indicated making tissue samples available, it was found that ductal lesions in patients with chronic pancreatitis exhibited K-ras mutations without additional indications of neoplastic transformation such as severe dysplasia or mutated p53 protein. Several earlier studies have histologically searched for possible carcinoma precursor lesions in chronic pancreatitis.^{153-156,179} Although two of these studies did not find severe ductal dysplasia or carcinoma in situ lesions and only observed hyperplastic or metaplastic ductal changes with no or occasionally mild dysplasia,^{155,156} the three others described cases with severe dysplasia in the chronically inflamed tissues. Cylwik et al¹⁵⁴ reported severe dysplasia in 9 percent of 70 resection specimens from patients with chronic pancreatitis; advanced fibrosis was associated with

dysplasia in 65 percent. On the other hand, using the WHO classification of pancreatic ductal lesions² Löttges et al¹⁷⁸ were unable to find any severe dysplasia or carcinoma in situ changes in 30 resection specimens from patients with various types of chronic pancreatitis and varying duration of the disease.

There is also a study showing that patients with chronic pancreatitis harbor significant chromosomal aberrations in the cells of their main pancreatic duct. These chromosomal abnormalities are similar to those observed in patients with pancreatic cancer.¹⁸⁰

CYSTIC FIBROSIS

Cystic fibrosis is the commonest recessive genetic disorder of Caucasians. Ninety percent of the diseased suffer from pancreatic insufficiency which usually begins in early childhood. As they are now possible to treat so they most often live up to the ages where pancreatic cancer appears. It has than been shown that these patients have an increased risk of pancreatic cancer.^{181,182} The cause of the observed excess might be the effect of the pathologic alterations in the gland caused by the cystic fibrosis process.

OCCUPATIONAL RISK FACTORS

Concerning occupational risk factors for pancreatic cancer there is a vast literature available, most of the somewhat difficult to total apprehend. Moreover, some of these studies discuss industrial processes that are not any longer in use. From an epidemiological point of view it is even more problematic that it is probable that almost only positive reports are published. That means that if a large number of studies show no relation between pancreatic cancer and some occupational factor there is a risk that the single positive study will be published and not the outnumbering negative studies. Also, in most studies, it has been difficult to control for smoker, the best documented risk factor for pancreatic cancer.

There is no proven relationship between the pancreatic cancer rate and the atmospheric pollution index or diverse industries.¹⁸³ As of 1973, Wynder et al³⁹ reported an abnormally high frequency of pancreatic cancer in workers and chemists exposed to naphthylamine and benzidine (benzidine alone does not seem to be a carcinogenic factor for the pancreas) but despite many studies of occupation and risk factors for pancreatic cancer, there has been no clear agreement about any specific occupation or industrial exposure as a risk factor for pan-

creatic cancer. Exposure to ionizing radiation or to DDT may cause pancreatic cancer, but other exposures are more controversial.^{184,185}

In one study occupation is considered to give a high risk of pancreatic cancer in managers and administrators, paper workers, engineers, dentists, chemists and electrical workers.¹⁶ However, it is difficult to interpret common etiological substances or working conditions from these occupations. In another study the mortality among aerial pesticide applicators compared to flight instructors had a risk ratio for pancreatic cancer of 2.7.¹⁸⁶

In a meta-analysis¹⁸⁷ of 92 studies covering 161 population in publications from 1969-98 exposure to chlorinated hydrocarbons (HC) solvents and related compounds was associated with a meta-risk ratio of 1.4 (95% confidence interval 1.0-1.8). Nickel and nickel compounds were considered in four populations (1.9; 95% CI 1.2-3.2). Excess risks were also found for chromium and chromium compounds (1.4; 95% CI 0.9-2.3), polycyclic aromatic hydrocarbons (PAHs) (1.5; 95% CI 0.9-2.5), organochlorine insecticides (1.5; 95% CI 0.6-3.7), silica dust (1.4; 95% CI 0.9-2.0), and aliphatic and alicyclic hydrocarbon solvents (1.3; 95% CI 0.8-2.8). Evidence on pancreatic carcinogenicity was weak or non-positive for acrylonitril, arsenic, asbestos, diesel engine exhaust, electromagnetic fields, formaldehyde, flour dust, cadmium and cadmium compounds, gasoline, herbicides, iron and iron compounds, lead and lead compounds, man-made vitreous fibers, oil mist, and wood dust. The occupational aetiological fraction of pancreatic cancer was estimated at 12 percent. In a subpopulation exposed to CHC solvents and related compounds it was 29 percent. To chromium and chromium compounds 23 percent, to nickel and nickel compounds 47 percent, to insecticides 33 percent, and to PAHs 33 percent. In a follow-up of workers in the Norwegian aluminium industry there was also an association between exposure to polycyclic aromatic hydrocarbons and pancreatic cancer.¹⁸⁸ There are also meta-analysis suggesting that cadmium is a plausible pancreatic carcinogen.¹⁸⁹

Among 2238 workers in a sulfite pulp mill in Denmark, followed-up 1955-1993, the overall cancer risk was close to the expected, but the standardized incidence ratio for pancreatic cancer was 1.9 (95% confidence interval 0.8-3.9).¹⁹⁰ There was also a significant association between exposure to leather dust with an odds ratio of 7.2 (95% confidence interval 1.4-35) in a Swedish case-control study of 2487 workers employed 1900-1989.¹⁹¹

Occupational exposure to p,p'-dichlorodiphenyl-trichloroethane (DDT) has also been associated with an increased pancreatic cancer risk. In an American study of 108 patients with pancreatic cancer and 82 control subjects the median serum levels of DDE, polychlorinated biphenyls (PCBs), and transnonachlor were significantly greater among cases than controls. A significant dose-response relationship was observed for total PCBs. Because pancreatic cancer is characterized by cachexia, the impact of this on the serum organochlorine levels in cases is difficult to predict. One plausible effect of cachexia is bioconcentration of organochlorines in the diminished lipid pool, which would lead to a bias away from the null.¹⁹² However, in a study of the adipose levels of DDT levels in population samples from 22 US states, comparing the 1968 levels with age-adjusted mortality rates between 1975 and 1994 no association was observed for pancreatic cancer.¹⁹³

A significant 2.3-fold risk (95% confidence interval 1.0-4.3) was found for pancreatic cancer among workers exposed to acrylamide, but there was no consistent exposure-response relations were detected (1787). The risk developing pancreatic cancer was increases 7.8 times (90% confidence interval 2.1-25.2) in persons exposed to asbestos in a ship yard.¹⁹⁴ In China an association was found between pancreatic cancer and employment as an electrician, with an increased risk for those exposed to electric magnetic fields. There was a threefold risk increase observed for men with the highest intensity.¹⁹⁵

A population-based case-control study based on death certificates from 24 US states included 63000 persons who died from pancreatic cancer occurring in the period 1984-1993 and 252200 controls died from causes other than cancer in the same time period. Industries associated with significantly increased risk of pancreatic cancer included printing and paper manufacturing; chemical, petroleum, and related processing; transport, communication, and public service; wholesale and retail trades; and medical and other health-related services. Occupations associated with significantly increased risk included managerial, administrative, and other professional occupations; technical occupations; and sales, clerical, and other administrative support occupations. Occupational exposure to formaldehyde was associated with a moderately increased risk of pancreatic cancer.¹⁹⁶

In a Finish study of 3922 male and 1379 female workers monitored for exposure to styrene, toluene, or xylene there was no increased risk for pancreatic cancer.¹⁹⁷ In a cohort of workers from three automobile manufacturing plants pancreatic cancer was associated with ex-

posure to synthetic fluids in grinding operations, with an odds ratio of 3.0 (95% confidence interval 1.2-7.5).¹⁹⁸

As there has been a sharp surveillance for a long term, but limited results, it appears that occupational exposure does not have a major etiological role for pancreatic cancer.

OTHER CARCINOGENS AND RISK FACTORS

All the known or suspected causes for pancreatic cancer (smoking, medical diseases, diet etc) explain only a fraction of the observed cases. Many additional cases are presumably related to genetic disorders. There are today indications for a genetic component in the etiology as there are familial aggregations of pancreatic cancer, although this could only be attributed to about 3 percent of all pancreatic cancers and show no change in frequency over the years.¹⁶⁴ Family occurrence of pancreatic cancer is rare,¹⁹⁹ but there are reports of pancreatic cancer in families.¹⁹⁹ In one study 8 of 71 unselected cases of pancreatic cancer had first-degree relatives with pancreatic cancer, and in another 17 of 80 cases had first- or second-degree relatives with cancer in other sites. Other studies have found aggregations of pancreatic cancer within kindreds. In one report, pancreatic cancer has been traced through three generations, including progeny from two of the progenitor's three marriages. In another large pedigree, pancreatic cancer was inherited in an autosomal dominant fashion accompanied by diabetes or pancreatic exocrine insufficiency.

Obviously, most cases of pancreatic cancer is of the sporadic form. However, during the last decade there are indications that there is also a familial form of pancreatic cancer. According to a study in Utah of 1108 patients the proportion of cases attributed to familial causes is approximately 8 percent, but the majority of the observed excess in familial cancer risk occurred at ages greater than 70. Those with a first-degree relative with pancreatic cancer had a relative risk of 1.18 (95% confidence interval 1.06-1.32). The strongest evidence for a genetic basis for some cases of pancreatic cancer comes from reports of aggregation of this tumor within families. For example, many members of the current French-speaking population of the province of Quebec, Canada, originated from a small group of French settlers who were geographically isolated for several generations. Inter-marriage could be the explanation for the frequency of familial pancreatic cancer in this region. In one report, patients with pancreatic cancer were 13 times more likely to have a family member with pancreatic cancer

than a group of matched controls. During the 1700s, a large group of the original French settlers in northeast Canada were forced to migrate to other regions and many eventually settled in Louisiana. It is suggested that the migrant from Canada carried their genetic susceptibility with them to the new location, where now a remarkably high frequency of pancreatic cancer is found.¹³⁶

Although most pancreatic cancers occurs sporadically, the disease may occur in family clusters, and often in association with several other specific hereditary disorders: hereditary pancreatitis, ataxia-telangectasia, hereditary non-polyposis colon cancer and familial atypical mole-malignant melanoma syndrome. Autosomal dominant transmission of pancreatic cancer can occur in isolated families in the absence of a known hereditary syndrome. Although environmental exposure common to affected family members may explain this clustering rather than hereditary factors, identification and study of the gene defects in these families may in the future enable at-risk individuals to be identified by genetic screening.³⁹ Most probably there will be found an interaction between hereditary and exogenous risk factors. There are several disorders that increase the risk of pancreatic cancer and have been defined on the genetic level: BRCA2, FAMM (familial atypical mole melanoma) syndrome, hereditary non-polyposis colon cancer, familial adenomatous polyposis, Li-Fraumeni syndrome, and the Peutz-Jeghers syndrome. The loci for the genes for all of these syndromes is now known, and all are believed to be autosomal dominant. BRCA2 is probably the most important, accounting for perhaps 5-10 percent of all sporadic cases of pancreatic cancer. There is also found a 5-10 fold increased risk in some families with one family member with pancreatic cancer but without the risk factors discussed above.¹³⁶ Altogether, genetic factors are known to play a significant role in perhaps 5 percent of the total pancreatic cancer burden.²¹⁰

There are some experimental data that ingestion of dietary fish oil enhances pancreatic carcinogenesis in azaserine-treated rats²¹¹ and probably in N-nitrosobis(2-oxypropyl)amine (BOP)-treated hamsters.²¹²

Among Chinese women, the risk of pancreatic cancer was significantly associated with number of pregnancies and live births. Compared with 0-2 pregnancies or live births, the odds ratio for 8 or more pregnancies and 5 or more was 1.9. A modest elevation in risk, women with a first birth at or before age 19 years relative to those at age 26 years or older. Ever use of oral contraceptives was also associated with excess risk.⁹¹

CONCLUSIONS

After 50 years of epidemiological studies of pancreatic cancer there are solid data only for smoking as the main etiological factor for exocrine pancreatic cancer in about one third of the cases, inherited factors in about five percent of the cases and chronic pancreatitis in an even smaller part. That leaves more than 50 percent in the category "unknown", which shall be looked upon as a challenge. It is probable that some dietary factor(s) will play a part, but these interactions are at best speculative today.

In the future it is probably most rewarding to connect the epidemiologists with the molecular biologists together with the clinicians to solve these problems. With a team-work approach also the etiology of pancreatic cancer can be explained, which is important if we shall reach better medical results in the future. Prevention, early diagnosis in distinct risk groups, and tailored treatment will then be cornerstones.

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