

Epidemiology and Prevention of Pancreatic Cancer

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Pancreatic cancer is an uncommon tumor, but because the mortality rate approaches 100%, this form of cancer has now become a common cause of cancer mortality. In the United States it is the fourth most frequent cause of cancer mortality; in Japan it ranks as the fifth commonest cause of death from cancer. Smoking is the major known risk factor for pancreatic cancer, accounting for ~25–30% of all cases. Some of the time-dependent changes in the frequency of pancreatic cancer can be explained by smoking trends. Aggressive public health measures to control smoking would substantially reduce the burden of pancreatic cancer. Dietary factors are less important for pancreatic cancer than for other digestive tract tumors, but consumption of a diet with adequate quantities of fruits and vegetables, plus control of calories either by dietary measures or by exercise will help to prevent this lethal tumor. There are more than a dozen inherited germline mutations that increase the risk of pancreatic cancer. Of these, hereditary pancreatitis confers the greatest risk, while BRCA2 mutations are the commonest inherited disorder. In addition to germline defects, there are several common polymorphisms in genes that control detoxification of environmental carcinogens that may alter the risk of pancreatic cancer. More research will be needed in this area, to explain and to clarify the interaction between genes and environmental factors.

Key words: pancreatic cancer – epidemiology – smoking – risk factors – genetics

INTRODUCTION

Pancreatic cancer, one of the most lethal of all human cancers, is now a common cause of cancer mortality in the United States and Japan. It is likely that in future decades, as longevity in these two countries increases, pancreatic cancer will become even more frequent.

Cancer epidemiology depends on accurate measurement of either incidence rates—the yearly occurrence of new cases in a specified group—or upon mortality rates. Because incident and mortality for pancreatic cancer are nearly identical, either measure can be used to study the frequency of this neoplasm.

Unfortunately, the pancreas, located in an inaccessible location within the abdomen, makes the diagnosis of pancreatic cancer more difficult than diagnosing other digestive tract cancers. This was especially true in previous decades, and many of the older reports must have included patients where the diagnosis was wrong. Newer diagnostic modalities developed within the past two decades have greatly improved the accuracy of diagnosis.

In this report we present updated information about the epidemiology of pancreatic cancer to help determine environmental or genetic risk factors that affect susceptibility to this tumor.

DESCRIPTIVE EPIDEMIOLOGY

FREQUENCY

In the USA a total of ~30 000 new cases of pancreatic cancer are diagnosed each year. The corresponding figure for Japan is ~19 700. However, because of the extreme lethality of the cancer, pancreatic cancer ranks as the fourth commonest cause of cancer death in USA males after cancer of the lung, prostate and colo-rectum; in females it is also the fourth commonest cause of cancer death after lung, breast and colo-rectum. In Japan it is the fifth most common cause of cancer death, preceded in males by lung, stomach, liver and large bowel, and in females by stomach, large bowel, lung and breast. In the USA male rates are ~40% higher than females rates; in Japan the corresponding figure is 70% (Table 1).

As with nearly all other types of digestive tract cancer, pancreatic cancer exhibits an uneven world distribution. Incidence rates in high-risk countries are about 5–7 times higher than incidence rates in low-risk countries with accurate cancer registration, implying that environmental factors play an impor-

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Table 1. Mortality from pancreatic cancer: comparison of Japan and USA

| | Japan (1999) | | USA (1998) | |
|---------------------------------------|--------------|---------|------------|---------|
| | Males | Females | Males | Females |
| No. of deaths | 10 204 | 8450 | 13 806 | 14 529 |
| Age-adjusted rate (world) per 100 000 | 8.5 | 4.8 | 7.3 | 5.3 |
| Percent cancer deaths | 5.8% | 7.4% | 4.9% | 5.6% |
| Cumulative death rate | | | | |
| (0–74) | 0.97% | 0.52% | 0.88% | 0.59% |
| (0–84) | 2.1% | 1.3% | 1.3% | 1.3% |

USA data from SEER Cancer Statistics Review (2) and Japanese data from Kakizoe (52).

tant role (1). Figure 1 lists male pancreatic cancer rates from selected world cancer registries where pancreatic cancer registration is based upon a sufficient number of patients to be reliable. The Japanese rates for males are now high, compared to other countries, and are similar to rates in the USA white population.

AGE OF ONSET

Pancreatic cancer is predominately a disease of older individuals. In the United States, only ~13% of all patients are diagnosed before 60 years of age, and nearly half of patients are ≥75 years at the time of diagnosis (2). A positive family history for pancreatic cancer or a genetic defect is often present in patients with an early onset of pancreatic cancer. At present, surgery offers the best chance for increased survival but, unfortunately, many of the patients in the older age groups have associated co-morbidities that increase the risk of complications and/or death.

RACIAL FACTORS AND PANCREATIC CANCER

Pancreatic cancer exhibits racial differences at the molecular level. For example, USA blacks have more frequent K-ras mutations to valine than Caucasians (3). Chinese patients with pancreatic cancer may have different expressions of Ki-ras and p53 than Western or Japanese patients (4,5).

In several publications, racial differences in survival have been recorded after treatment of pancreatic cancer. In particu-

lar, Asian patients appear to have a better survival rate than non-Asian patients. Clinicians have suspected these differences may be related to early or late diagnosis or, perhaps, to the extent or the type of operation performed. Longnecker and colleagues (6) studied over 10 000 patients with pancreatic cancer reported to the USA SEER cancer registry during the period from 1973–1995. They found that Asian patients tended to have less aggressive tumors than either white or black patients. The explanation for this unexpected finding is unclear: all of the study patients resided in the USA, but there could be race-related genetic factors or differences in environmental exposure that determine survival.

TIME TRENDS

Will the number of patients diagnosed with pancreatic cancer increase or decrease over the next few decades? Cancer rates increase rapidly with age, the strongest risk factor for all digestive tract tumors. Based simply upon the expected increase in number of persons >65 years in the population of most countries, we can anticipate a measurable age-related increase in the global burden of pancreatic cancer.

Smoking is the other major factor influencing the frequency of pancreatic cancer (see below). In populations where smoking has increased, such as Japan, the frequency of pancreatic cancer increased from the 1950s to about 1990 and has now leveled out; in populations where smoking rates are decreasing—i.e. USA white males, pancreatic cancer is declining (Fig. 2). Mulder and colleagues used Markov multi-state computer models based on country-specific data to estimate the impact of smoking cessation on the frequency of pancreatic cancer in the European Union (7). If all current smokers suddenly ceased smoking, the estimated number of new patients in the EU up to 2015 would be reduced by 150 000—or ~15% of the anticipated total. A more realistic goal (reducing smoking prevalence by ~45% in males and 30% in females) leads to a reduction of almost 30 000 male and 10 000 female patients. Clearly, quitting smoking results in a sizeable reduction in pancreatic cancer, but will require aggressive government action.

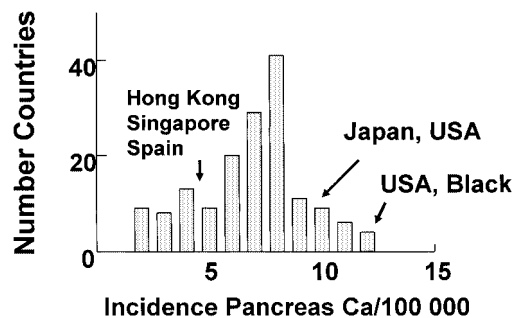


Figure 1. Histogram displaying international frequency of pancreatic cancer. Rates in Japan and USA (Caucasians) are higher than most other countries, but rates in USA Blacks are higher still (1).

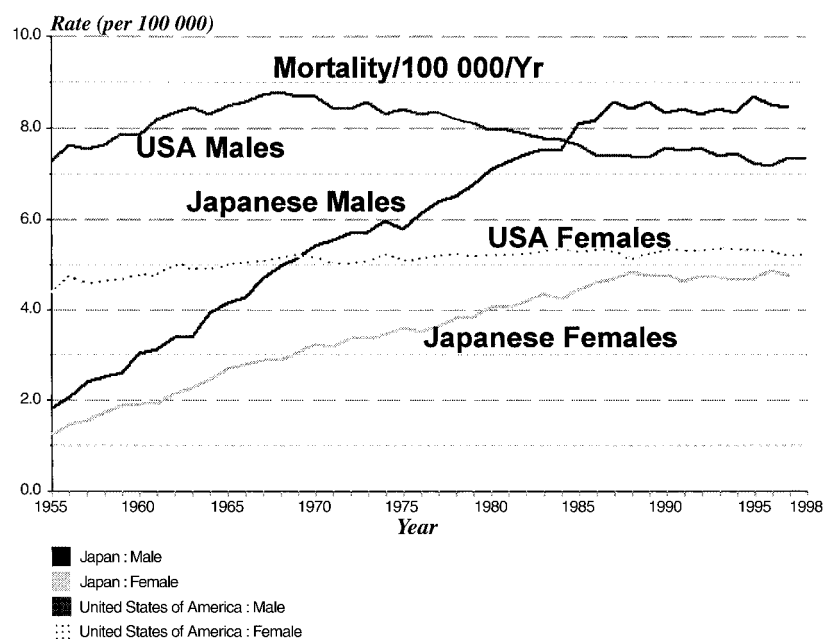


Figure 2. Time trends for pancreatic cancer in Japan and USA: 1955–1998. In Japan, rates are increasing for both males and females. In the USA male rates are decreasing, but there is a slight increase in female rates. From Kokawa et al. (50) and Anderson et al. (51).

ENVIRONMENTAL RISK FACTORS

SMOKING

Smoking is the strongest environmental risk factor known to cause pancreatic cancer. Carcinogens derived from tobacco smoke probably reach the pancreas via the bloodstream after being absorbed from the lungs or from the upper aero-digestive tract. In addition, there is a possibility that ingested tobacco products reach the pancreas directly after reflux into the pancreatic ductal system from the duodenum. If this mode of exposure is correct, it could partly explain the large number of pancreatic cancers that occur in the head of the pancreas.

Nearly all published reports show that exposure to tobacco products increases the risk of pancreatic cancer, usually with about a 2-fold increased risk, compared to non-smokers. The findings in studies performed in various countries are highly consistent. In the USA several case-controlled studies show a strong relationship between smoking and pancreatic cancer (8,9). In the UK, Doll et al. reported the results of a 40-year study of British physicians (10). They noted that annual male mortality rates for pancreatic cancer in non-smokers, ex-smokers and current smokers were 16, 23 and 35 per 100 000 man-years, respectively. In Japan, two cohort studies have demonstrated an increased risk of pancreatic cancer in smokers: both studies found a clear dose response (11,12). Most reports demonstrate a graded dose response, with heavy smokers having a substantially higher risk of pancreatic cancer than light smokers.

What proportion of pancreatic cancer is caused by smoking? We can estimate the smoking attributable risk, the proportion

of pancreatic cancer caused by smoking, using the following formula (13):

$$\text{Attributable risk} = P(RR - 1) / [P(RR - 1) + 1]$$

where P is the proportion of the population who smoke, and RR is the relative risk of pancreatic cancer in smokers compared to non-smokers. If P, the prevalence of smoking is ~30–35%, and RR = 2, then the estimated attributable risk is ~25%.

DIET

Epidemiologists have long suspected that the striking international differences in the frequency of digestive tract tumors are caused by dietary factors. For the pancreas there are data to suggest that dietary items either increase or decrease the risk of pancreatic cancer. Increased caloric content of the diet has been linked to several types of cancer, including pancreatic cancer. In particular the fat content of the diet, which contributes heavily to the overall caloric intake, is a suspected risk factor. In contrast, increased consumption of fruits and vegetables may reduce the risk of pancreatic cancer (14–18).

A large proportion of the adult population takes daily vitamin pills or dietary supplements. But do these medications prevent pancreatic cancer? Two antioxidants, alpha tocopherol and beta-carotene, have been evaluated in a prospective study of male smokers: these substances did not reduce the frequency of pancreatic cancer over a follow-up period of 5–8 years (19).

One of the particular problems encountered in trying to link pancreatic cancer to diet is to do with the rapid clinical course of the disease. Most studies of risk factors for pancreatic cancer are case-control studies, but at the time of case ascertainment,

Table 2. Germline diseases associated with pancreatic cancer

| Disease | Affected chromosome | Remarks |
|--|---|--|
| Familial pancreatic cancer (USA National Familial Pancreatic Tumor Registry) | ? | 5–10-fold risk for first degree relatives (53). |
| Familial pancreatic cancer (Seattle cohort) | 4q32–34 | High risk of pancreatic cancer, pancreatitis and diabetes. Smokers develop early onset pancreatic cancer (48). |
| Hereditary nonpolyposis colon cancer (HNPCC) | 2, 3 | Some persons may develop pancreatic cancer (54). |
| Von Hippel–Lindau syndrome | 3p25 | Neuro-endocrine tumors of pancreas are frequent (55). |
| Familial adenomatous polyposis | 5q12–21 | Mutation found in pancreas and in ampullary cancers (56). |
| Hereditary pancreatitis | 7q35 | Cumulative risk of pancreatic cancer at least 30% (35). |
| Familial atypical malignant melanoma syndrome | 9p21 | Patients carrying the p16 Leiden mutation have a 17% cumulative risk of pancreatic cancer (57). |
| BRCA2 | 13 | Most common inherited mutation leading to pancreatic cancer (58). |
| Peutz–Jeghers syndrome | 19p | Mutation may contribute to both sporadic and inherited disease (59). |
| Cystic fibrosis | 7q31 | Increased risk of digestive cancer, including pancreatic tumors (60,61). |
| Ataxia-telangiectasia | 11q | Breast cancer is most common tumor; a few patients with pancreatic cancer (62). |
| Li–Fraumeni syndrome | 17p13.1 | Defect in <i>p53</i> . Moderate increased risk of pancreatic cancer |
| Fanconi anemia | Multiple chromosomes including 3p22–26, 9p13, 9q22.3, 16q24.3 | A few patients <50 years with pancreatic cancer carry FANCC or FANCG genes (63). |

many patients are unable to respond to detailed dietary questionnaires. Dietary data obtained from spouses or family members is likely to be inaccurate (20). Of the various dietary components that have been studied in relation to pancreatic cancer, the fat content of the diet seems to be the component that has most consistently been associated with pancreatic cancer (14,16,21,22). In Japan, consumption of meat, which has a high fat content, increased the risk of pancreatic cancer; traditional Japanese food, such as tofu and fish, reduced the risk (23).

An increased intake of calories causes obesity, which several studies have shown to increase the risk of pancreatic cancer. Exercise, which helps to maintain normal body weight, has been associated with a reduced risk of pancreatic cancer in some (22), but not all (24), studies.

Alcohol is a major risk factor for pancreatitis, but does it cause pancreatic cancer? Nearly all studies fail to support this association, including a recent large retrospective cohort study from Sweden (25). Coffee, another widely consumed beverage is also unlikely to cause pancreatic cancer.

OCCUPATION AND PANCREATIC CANCER

Certain jobs involve exposure to carcinogens such as chlorinated hydrocarbons, formaldehyde, pesticides, organochlorines and other various substances, which could result in an increased risk of pancreatic cancer (26–33). But the contribution of occupation to pancreatic cancer is small—probably no more than 5%. In many of the reports, data on exposure to carcinogens has not been adjusted for smoking or other variables.

PRE-EXISTING DISEASES AND RISK OF PANCREATIC CANCER

All types of chronic pancreatitis (alcoholic, non-alcoholic, hereditary, tropical) have been linked to the subsequent development of pancreatic cancer (34–36). Pre-existing alcoholic and non-alcoholic chronic pancreatitis result in about a 10–20-fold increased risk of pancreatic cancer. For tropical and hereditary pancreatitis the risk is much higher, probably because the onset of disease usually occurs early in life. The cumulative risk of pancreatic cancer in patients with hereditary pancreatitis is ~30–40%, higher than for any other known causative factor. Cystic fibrosis affects the digestive tract, including the pancreas: a few patients with pancreatic cancer have been reported with this recessive genetic disorder.

Are there other digestive tract diseases with an increased risk of pancreatic cancer? Both gallstone disease (37–40) and peptic ulcer disease (41–43) have been suggested as possible pre-existing diseases that might cause pancreatic cancer, but the evidence is weaker than for chronic pancreatitis. Data confounded by smoking might explain the putative association between peptic ulcer disease and pancreatic cancer.

Diabetes afflicts ~5% of the adult population. Is this common metabolic disorder related to pancreatic cancer? It has been difficult to establish this link, since diabetes can be one of the early manifestations of pancreatic cancer. A meta-analysis published in 1995 suggested that diabetics have about a 2-fold increased risk of pancreatic cancer (44); most subsequent studies have confirmed this link.

Table 3. Genetic polymorphisms and pancreatic cancer

| System | Findings |
|---|---|
| Cytochrome P-450 <i>N</i> -acetyltransferase | Conflicting evidence. Increased frequency in pancreatic cancer (64). No significant association (65). |
| Glutathione <i>S</i> -transferase (GST) | Inconclusive evidence (66). |
| Uridine 5'-diphosphate glucuronosyltransferases (UGT) | GSTT1 deletion and heavy smoking increased the risk of pancreatic cancer (65). |
| | UGT1A7*3 allele with low detoxification activity doubles risk of pancreatic cancer (67). |

INHERITED DISEASES AND PANCREATIC CANCER

There is a growing list of germline diseases that markedly increase the risk of pancreatic cancer (Table 2). Undoubtedly the most important inherited germline disorder is BRCA2 which is found in ~7–10% of patients with sporadic pancreatic cancer and 15–20% of patients where there is a strong family history (45,46). Most of the diseases listed in Table 2 are inherited in an autosomal dominant pattern except for ataxia-telangiectasia, cystic fibrosis and Fanconi anemia, which are autosomal recessive diseases.

GENETIC POLYMORPHISMS AND PANCREATIC CANCER

Mutations which occur with a frequency of >1% in the population are referred to as polymorphisms. There are several polymorphic genes with the potential to detoxify tobacco or diet-related carcinogens and thereby protect the pancreas from oxidative stress. The results of studies looking at genetic polymorphisms and pancreatic cancer are shown in Table 3. Since there are racial differences in the frequency of various polymorphisms, and since risks are likely to differ according to smoking status, these two variables must be included in meaningful studies of pancreatic cancer and genetic polymorphisms. More studies need to be done in this area because polymorphic genes could explain why many persons exposed to known risk factors do or do not develop pancreatic cancer.

GENE-ENVIRONMENT INTERACTION

Since both inherited genetic factors and environmental factors are known to cause pancreatic cancer, some, or perhaps all, patients with pancreatic cancer will have both types of exposure. Can the impact of multiple exposures be quantitated? How do we measure interaction? Patients with the hereditary form of pancreatitis are known to have an extremely high risk of pancreatic cancer—almost 50 times greater than the background rate. Patients with this disease who smoke develop pancreatic cancer around age 50, two decades earlier than patients with the same mutation who are non-smokers (47). Similar findings have been observed for a group of patients with familial pancreatic cancer in the northwest of the USA. Rulyak et al. have reported that within this high risk group, smokers develop pancreatic cancer about 10 years earlier than non-smokers (48).

PREVENTION AND SCREENING ISSUES

Would screening improve the extremely low survival rate after the diagnosis of pancreatic cancer? Because the disease is relatively rare, it would be inappropriate to subject the entire population to screening, as suggested for breast, colon and prostate. A recent consensus conference (49) suggested that it would be appropriate to screen patients with hereditary pancreatitis—a group at high risk of pancreatic cancer—at ≥40 years of age. Preferably, such screening would be performed at a few selected centers in a research setting. The exact screening procedure (EUS, helical CT or MRI/MRCP) needs further evaluation.

Chemoprevention, with agents such as COX inhibitors would benefit persons at high risk for pancreatic cancer (50). Aspirin has been shown to reduce the risk of pancreatic cancer in some studies (51). These findings need to be verified in a randomized controlled clinical trial.

SUMMARY

In view of the high mortality for pancreatic cancer, an important strategy for reducing the burden of this cancer is to understand, and, if possible, reduce exposure to known risk factors. High priority should be given to efforts to control smoking, because smoking is known to double the risk of pancreatic cancer. Rates for pancreatic cancer in the USA are currently declining in males but not females, presumably because of changes in smoking habits. In Japan, where smoking is still prevalent, pancreatic cancer rates increased until 1990; both male and female rates have stabilized since then. At the present time, reducing the prevalence of smoking is the single most effective measure to prevent this lethal tumor.

Diet is not as strong a risk factor for pancreatic cancer as smoking, but consuming a 'prudent' diet containing ample fruits and vegetables, moderate fat content and without excess calories, will help to avoid obesity and might reduce the risk of pancreatic cancer.

Genetic factors play an important role in the genesis of pancreatic cancer. More than 12 germline disorders are known to be associated with pancreatic cancer, with BRCA2 being the most frequent. Although these inherited genetic disorders are thought to cause only about 10% of the total burden of pancreatic cancer, additional research focusing on patients with a strong family history of pancreatic cancer is likely to benefit the much larger group of patients with sporadic pancreatic cancer.

There are no entirely effective screening strategies currently available, even for persons with an exceptionally high risk of pancreatic cancer. For patients with hereditary pancreatitis or for kindreds where there are multiple family members with pancreatic cancer, screening techniques, such as endoscopic ultrasound and spiral computerized tomography offer promise, but have not been fully evaluated for the detection of early pancreatic cancer in these populations.

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