Pancreatic cancer: any prospects for prevention?

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Summary
Primary prevention of pancreatic cancer and public health measures to reduce its incidence are dependent on data from epidemiological studies. Currently, the only definite risk factor is smoking, although a diet rich in fruit and vegetables may be protective. The K-*ras* mutation may have a role in diagnosis and screening.

Carcinoma of the pancreas is a devastating illness[1][2] with fewer than 0.4% of patients alive 5 years after diagnosis.[2] As the prospects for cure are minimal, an understanding of its aetiology is essential to identify reversible risk factors. This article describes the epidemiological studies which are contributing to our understanding of the causation of this disease, which in turn should lead to prevention measures.

The distribution of the disease

Carcinoma of the pancreas is customarily defined as a malignant neoplasm of the exocrine pancreas with 85% of lesions originating from the ductal epithelium.[3] Each year there are approximately 185 000 new cases worldwide, making it the 13th commonest cancer and the 8th most frequent cause of cancer mortality.[4] To help reduce this high disease burden through an understanding of its aetiology, it is first essential to collect temporal incidence data from different populations. Incidence data is important because it identifies groups at high risk in whom aetiological factors may be more easily identified. Secondly, such data are valuable because marked changes in a given population over a short time period suggest a predominantly environmental rather than a genetic cause.

Incidence data on pancreatic cancer is available from the Cancer Incidence in Five Continents Series, which collects information from cancer registries around the world.[5] The series standardises incidence to a world population, allowing comparisons between countries and observation of temporal trends. All registries collect demographic data and code cancer site according to the standard International Classification of Diseases.[6] The data collection procedure is thorough, with most registries analysing multiple registration methods including in-patient and out-patient notes, general practitioner records, death certificates and data from radiotherapy and pathology departments. To prevent duplication of information, the registries employ multiple cross-checking with nearly 80% using a computerised system. Consequently the data obtained are comprehensive and frequently used for epidemiological studies.

The incidence of pancreatic cancer is highest in North America and in New Zealand Maoris (6–11 cases/100 000 population), intermediate in Europe and Japan, and lowest in Africa and the Indian sub-continent (<1.5 cases/100 000).[5] The disease is approximately 30% more frequent in men than women across regions and is rare before the age of 45 years, but increases dramatically with age. In Britain, the most recent data show the age-standardised incidence to be 7.4/100 000 in men and 5.3/100 000 in women.[7] Racial differences exist in incidence, for example in the US, where pancreatic cancer is more common by 40% in blacks than whites.[5] Studies reporting socioeconomic status and incidence give conflicting results, although two studies noted a slight increase in the higher social classes[8][9] and with increasing educational level.[8] Occupational reports have shown links between pancreatic cancer and petrochemical workers, chemists, public administrators, radiologists and nuclear energy workers. However, for each workplace, there are other reports not confirming the links.[10] Consequently, the inconsistency of the evidence argues against occupational factors being important in aetiology.

Temporal changes in incidence have varied across the world. The incidence in countries with a high prevalence such as Britain and the US has tended to level in the past 20 years in men, but is still rising in women.[11] The dramatic rise in countries such as Japan, which has noted a third more cases during the last decade, suggests environmental factors are more important than genetic ones, although familial clustering is described.[12][13] The case for environmental risk factors is further strengthened if changes in such factors over time correlate with temporal incidence variations and also explain differences between groups such as men and women.

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Difficulties in studying pancreatic cancer

Although the histological definition of the disease is precise, there are several major problems in studying its epidemiology. Firstly, due to the gland's anatomical position, it is technically difficult to obtain tissue to verify the diagnosis. Secondly, as the disease frequently presents at an advanced stage, diagnostic intervention may be inappropriate as only palliative treatment can be offered. Consequently, the disease is often registered on the basis of clinical suspicion, introducing error in case definition. In the British registries, histological verification was achieved in only 33% of cases and the figure is lower elsewhere.[5] Another difficulty is recruiting sufficient patients for study after diagnosis, as the survival time is short. This problem can be overcome by using proxy respondents, although this itself may result in errors in measuring risk factors such as diet. Previous work has shown proxy respondents under-report total food intake but give accurate estimates of the proportions of nutrients.[14] A further problem in studying the epidemiology is that, in the small number who survive for 5 years, the initial diagnosis is frequently incorrect. For example, a retrospective review of cases from Finland between 1975 and 1984 showed 42% of 78 long-term survivors did not have any confirmatory histology and in half of the remainder, the original histological diagnosis was incorrect on review.[15] However, current and future epidemiological studies should be helped by the wider availability of diagnostic endoscopic retrograde cholangiographic pancreatography and imaging procedures which are non-invasive such as ultrasound, computed tomography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography.

Deciding which risk factors to investigate

Clues as to the aetiology of pancreatic cancer can be provided by descriptive studies which measure and correlate exposures with incidence. Armstrong and Doll[16] correlated pancreatic cancer incidence in 23 countries with diet and showed positive associations with animal protein, eggs, and sugar. This information helps justify future work investigating diet, although its validity is dependent on the accuracy of both cancer registration and dietary data from each country. Migrant studies can also generate hypotheses, although in pancreatic cancer the observations are conflicting. For example, death rates in migrants from Europe to Australia, showed rates declining to those of the host population in migrants from Britain, but increasing in populations from continental Europe.[17] In this study, mortality rather than incidence was measured, although both are probably similar. Cultural differences such as language may have inhibited continental migrants from using medical services.

Another potential source of information on aetiology may be provided by looking for associated diseases. If the risk factors for the concomitant illness are known, these may also be shown to be involved in pancreatic cancer. For example, chronic pancreatitis has been associated with pancreatic cancer, and in the former alcohol is the major risk factor. However, deciding whether or not chronic pancreatitis is a true risk factor is difficult because of the absence of large prospective studies in this area. Lowenfels *et al*[18] conducted a multicentre historical cohort study and reported a standardised incidence ratio of 14.4 for subjects followed for 5 years or more. However, there were considerable methodological problems including poor case verification and lack of measurement of other potential risk factors in many patients.

Diabetes mellitus is often quoted as being associated with pancreatic cancer, although this is now thought to be unlikely. A meta-analysis of 20 studies did report a pooled relative risk of 2.1 (95% confidence interval (CI) = 1.6–2.8), although 11 reports had confidence interval limits below one and several cohort investigations did not find an expected increasing risk with increasing duration of diabetes.[19] The largest case-control study found an odds ratio of 3.04 (95% CI = 2.21–4.17) for diabetes in patients who developed cancer within 2 years of the diagnosis of diabetes.[20] However, when analysed for diabetes of 3 or more years duration the odds ratio was insignificant (odds ratio 1.43, 95% CI = 0.98–2.07). Furthermore, the risk of pancreatic cancer decreased with increasing duration of diabetes, which has been confirmed in other studies.[21] There is also laboratory evidence which argues against diabetes mellitus being a true risk factor. Here, recent work has shown that neoplastic pancreatic tissue produces excess islet amyloid polypeptide (IAPP)[22] which increases insulin resistance and gives rise to hyperglycaemia. This 37-amino acid polypeptide is produced in the beta cells of the islets and its plasma concentration is increased in patients with pancreatic cancer compared with patients with other cancers or no cancers. A role for IAPP

Table Mortality in British male doctors from pancreatic cancer by smoking status

Smoking status	Annual mortality per 100 000
Non-smoker	16
Former smoker	23
Current smoker	35
1–14 cigarettes per day	30
15–24 cigarettes per day	29
>25 cigarettes per day	49
Pipe and cigar smokers	24

p-value for the standardised test for trend was p<0.001; from Doll *et al*, 1994[32]

is supported by the observation of improved glucose tolerance and insulin sensitivity after subtotal pancreatectomy, despite reduced insulin secretion.[23]

An increased risk of pancreatic cancer of a magnitude 2.5–7 is consistently observed after gastrectomy. A prospective study of 34 000 Californian Seventh-day Adventists found a relative risk of 2.62 (95% CI = 1.0–6.9) with surgery for peptic ulcer.[24] A large case-control study[25] reported an odds ratio of 5.3 (95% CI = 1.6–21.5) and a follow-up cohort of 700 men post-gastrectomy found 11 cases of pancreatic cancer against an expected four.[26] Importantly, two of these studies adjusted for the potential confounding effect of cigarette smoking in patients post-surgery.[24 25] No definitive biological mechanism has been proven for the association and on a population basis it is of little significance.

In the search for exposures which explain the incidence patterns and changes in pancreatic cancer, risk factors should be studied that have also altered in countries and in specific groups. The two most plausible factors which could explain part of the demographic patterns are smoking and dietary habits.

Smoking is a causative agent

The effect of cigarette smoking on pancreatic cancer has been thoroughly investigated and in 1985 the International Agency for Research on Cancer (IARC) declared "cigarette smoking is an important cause of pancreatic cancer".[27] The evidence to support this statement comes from both epidemiological and laboratory studies. Four large case-control studies, which used controls without tobacco-related disease, showed odds ratios of between 1.4 and 3.6 for consuming over 20 cigarettes daily and a general dose-response effect.[28–31] The findings from these case-control studies have been confirmed in cohort investigations which calculated a more precise relative risk and reduce study error by lowering recall bias of smoking habits. The cohort study of Doll *et al*[32] in British male doctors measured smoking and disease incidence and has the largest follow-up period, namely 40 years, of any prospective investigation. The study reported a significant positive trend (p<0.001) between cigarette consumption and mortality from pancreatic cancer, with men smoking more than 25 cigarettes daily at three times greater risk than non-smokers (table). The risk was also increased in other types of smoking and for all types decreased on cessation of the habit. Other cohort studies from North America,[33] Japan,[34] and Sweden[35] have shown similar dose-response effects of similar magnitudes. This epidemiological evidence is supported by animal studies which showed nitrosamines in tobacco induced pancreatic tumours.[36] The mechanism of how smoking causes cancer is unknown, but carcinogens could theoretically reach the pancreas via the blood or refluxed bile. The proportion of pancreatic cancers due to smoking is difficult to determine partly because smoking habits vary over time. However, a crude estimation using data from the British male doctors study[32] suggests that about 45% can be attributed to smoking. Clearly, efforts to encourage the population to cease smoking are required to reduce the incidence of pancreatic cancer.

Is diet important?

Diet is a credible risk factor to investigate in the aetiology of pancreatic cancer and evidence is beginning to emerge that a high fruit and vegetable intake may be protective. Fruit and vegetables contain many chemicals with potential anti-cancer properties including carotenoids, vitamins C and E, flavonoids, selenium and plant sterols. Important information on diet has been provided by a large case-control study under the direction of the IARC.[37] Here, centres in Canada, Holland, Australia and Poland collected data on 800 cases and 2000 controls. The combined analysis showed the relative risks by quintile of total energy intake were 1.22, 1.20, 2.00, and 2.07, relative to the first quintile, this trend being highly statistically significant (p<0.0001). Total energy must be corrected for when analysing particular foods, to determine the effect of the food itself rather than its energy value.[38] The SEARCH programme showed statistically significant relationships between pancreatic cancer and increasing carbohydrate intake and a decreasing risk with fibre intake and vitamin C. There was no relationship with total or saturated fat intake, protein intake or beta-carotene. A further 10 case-control studies have supported this protective effect of fruit and vegetable consumption.[39] The advantages of such case-control studies are that they can be completed relatively quickly on diseases which may take many years to develop. However, their major drawback is recall bias, where participants may have difficulty recalling past dietary habits before they developed disease. Furthermore, subjects tend to report current rather than past diet which may be influenced by their current illness.

More accurate information on diet is provided by cohort studies which record current food intake in healthy subjects before they develop disease. Several cohort investigations on pancreatic cancer are in progress and three have reported.[24][34][40] One large cohort of 260 000 Japanese subjects, with 679 cases developing over 17 years, showed a positive association with red meat, although this just failed to be significant[34] (p=0.063). No association with vegetables was reported, although the dietary questionnaire used was too crude to measure vegetable intake reliably. Another cohort study of 14 000 residents of a retirement community reported a non-significant negative association with fruit and vegetable consumption[40] and a cohort of 34 000 Seventh Day Adventists found a significant protective effect of dried fruit and vegetables.[24] In general, the studies demonstrating a protective effect of fruit and vegetables suggest they may reduce the risk of pancreatic cancer by between one-third and two-thirds.[24][37][40] To date, the association with red meat reported by some[25][41] but not all[37] case-control studies has not been equivocally confirmed by data from cohort studies.[24][34] However, larger cohort studies with accurate dietary measures are needed and these are now in progress. The largest of these is the European Prospective Investigation into Cancer and Nutrition study (EPIC), which will investigate the relationship between diet, life-style and the incidence of cancer, including pancreatic cancer.[42] EPIC will recruit approximately 400 000 men and women aged 35 to 70 years and is now in progress in centres in nine European countries. Other prospective dietary studies are also being conducted in the US[43][44] Canada[45] and The Netherlands.[46] All these studies will help determine if there is a true relationship between diet and pancreatic cancer and confirm whether a high fruit and vegetable intake is protective.

Beverages and aetiology

An association between coffee and the disease was raised in 1981 when a case-control study by MacMahon *et al* showed those consuming three or more cups per day had a relative risk of 2.7 (95% CI = 1.6–4.7) compared to non-coffee drinkers.[31] However, subsequent cohort studies showed no association and the data from most other case-control studies has not shown a link.[47] A particular problem in studying coffee is the confounding effect of smoking, as increased coffee drinking can be associated with smoking. Due to the inconsistencies in the available evidence, coffee cannot currently be regarded as a definite carcinogen. However, coffee contains over 700 compounds and its pattern of drinking is diverse, so maybe a future association will be shown with a particular type of coffee drinking. The effect of tea was investigated in the retirement community cohort and a significant protective trend was observed.[40] However, the majority of other epidemiological studies have not confirmed this finding and tea is not regarded as being protective against pancreatic cancer.[25][48]

Alcohol is often thought of as a risk factor for pancreatic cancer although most studies do not support this. The large Japanese cohort study[34] found no association between total alcohol intake and mortality, although there was a positive association in the sub-group of whiskey drinkers (relative risk 2.78, 95% CI = 1.24–6.15). The prospective retirement community investigation found no relationship with alcohol[40] and the one in Seventh Day Adventists did not provide information as its members generally abstain from alcohol.[24] Importantly, the two studies investigating alcohol[34][40] adjusted for cigarette smoking, as the consumption of the two is closely related. The lack of a consistent association from these studies and the fact that only one of 14 case-control investigations found an association, led the IARC to conclude there was little evidence for a causal association.[49]

The genetic epidemiology

Genetic epidemiology will contribute to understanding the disease's aetiology by investigating genetic and molecular changes in relation to risk factors. The commonest genetic abnormality in pancreatic cancer is a mutation of the K-*ras* proto-oncogene which encodes a protein involved in cell growth and differentiation. A review of six studies[50] found this mutation in a mean of 84% of cases (range 71–95%). Supportive evidence for the importance of this mutation was that normal tissue did not contain K-*ras* mutations and the abnormality was also found in other human neoplasms. An American study[51] showed the prevalence of K-*ras* mutations in adenocarcinomas of the pancreas in patients who smoked was 88% compared to 68% in non-smokers (p=0.046). This correlation between smoking and genetic changes strengthens the evidence for smoking being causative. Similar evidence is needed for other potential risk factors such as diet. Tumour suppressor gene mutations and deletions also occur in pancreatic

neoplasia including in the genes p16^{INK4A}, TP53 and the DPC4 gene. DPC4 (deleted in pancreatic cancer) is a tumour suppressor gene located on chromosome 18 and mutations may play a role in activation of pancreatic carcinogenesis.[52] Large prospective studies such as EPIC routinely take plasma samples for analysing biomarkers such as nutrients and hormones and will be able to see if these correlate with genetic changes in patients developing disease.

Prospects for prevention

The lack of curative treatment for most patients with pancreatic cancer emphasizes the importance of understanding the aetiology of the disease so that prevention strategies can be developed. Currently, the only definite carcinogens are those in cigarettes, so public health programmes to discourage smoking are vital to prevent pancreatic cancer among others. This will require action and policies to reduce smoking by both governments and health educational authorities. In Britain and the US, advertising on smoking and the number of public places permitting smoking are decreasing, so this may contribute to a future decline in incidence. Data are accumulating that fruit and vegetables are protective, although confirmatory evidence is required from the large prospective trials currently underway. These studies should report early in the new millennium and if they show fruit and vegetables are important, then a further opportunity for prevention is available.

No screening tests for pancreatic cancer are routinely available, although K-*ras* mutations occur in DNA from pancreatic juice, peripheral blood and stools of patients with the disease.[53] This offers an exciting prospect for future research, although there will be problems in designing a sensitive and cheap test to perform in positive individuals and in increasing the sensitivity of the screening test itself. Therefore, the current emphasis is on primary prevention and developing public health measures based on consistent epidemiological evidence. Clinicians have an important part to play in future research by developing simpler and less invasive diagnostic tests, which will not only benefit patients, but lead to accurate disease identification of patients for entering into aetiological studies.

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