

Pancreatic adenocarcinoma: epidemiology and genetics

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Abstract

Pancreatic adenocarcinoma is an important cause of death from cancer throughout the developed world. There are few established environmental risk factors, but a previous history of pancreatitis and exposure to tobacco and salted food appear to be the most important. A family history of pancreatic adenocarcinoma is not common in patients with this disease, but recent research has shown that pancreatic adenocarcinoma can be a feature of cancer susceptibility syndromes associated with germline mutations in p16, BRCA1, BRCA2, and APC. This highlights the need for a full family history in apparently sporadic cases. Somatic mutations in p16, BRCA2, and APC have also been reported in pancreatic cancer; however, K-RAS mutations appear to be the commonest oncogenic alteration. Recent advances in our understanding of the basis of hereditary cancer syndromes may be applicable to the diagnosis, treatment, and possibly prevention of pancreatic adenocarcinoma in the future.

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Incidence, prevalence, and mortality

There were approximately 185 000 new cases of pancreatic cancer world wide in 1980.¹ This number represents 2.4% of all cancers, but the disease is most common in developed countries.^{1,2} The highest age adjusted incidence rates are observed in Japan, eastern Europe, and North America (range for males 8.7-9.1, females 5.2-6.2 per 100 000) and the lowest age adjusted incidence rates are seen in north and west Africa and southern Asia (range for males 1.0-1.2, females 0.7-2.0 per 100 000).² Some of these differences may be attributed to reporting bias, but they are probably too large to be the result of biases alone.

According to Canadian national statistics, it is estimated that 2950 Canadians will die of pancreatic cancer in 1996.³ This will represent 4.8% of all cancer deaths. Pancreatic cancer is the fifth commonest cause of cancer death in both men and women. Among Canadians, the lifetime probability of developing pancreatic

cancer is just over 1%, and has been increasing slightly over the last 20 years. Prevalence data confirm that the national five year survival is less than 10%.

Clinical features of pancreatic cancer

DIAGNOSIS

Detection of adenocarcinoma of the pancreas at an early, treatable stage is difficult because the disease lacks specific signs and symptoms. The cardinal features are pain, weight loss, and jaundice. Patients do not often survive longer than one year after diagnosis; early diagnosis is crucial to improving prognosis for pancreatic cancer patients. Diagnostic methods currently used include endoscopic and percutaneous ultrasonography, computerised tomography (CT), fine needle aspiration, CT guided fine needle aspiration, angiography, and endoscopic retrograde cholangiopancreatography.⁴

TREATMENT

Treatment for pancreatic cancer is largely palliative since only 10-20% of pancreatic carcinomas are resectable and potentially curable, with a five year survival rate of only 4%. Surgical resection is the only curative treatment option available to date. It is usually combined with other forms of therapy such as preoperative, intraoperative, or postoperative radiation therapy. The tumour has a high resistance to chemotherapeutic agents. Strictly palliative therapies include bypass surgery and endoprosthesis insertion for the relief of pain and obstructive jaundice, as well as analgesic drugs and nerve blockades.⁴

PROGNOSIS

The case/fatality ratio is 1 for pancreatic cancer; this is higher than for lung cancer (0.84) and brain tumours (0.68).³ The average survival after diagnosis is less than six months; one year survival is less than 10%. In a review in 1977 it was noted that only 10% of patients were diagnosed at stage I of the disease. Of these, 40% lived for six months, 20% for one year, and only 2% survived for five years. In the vast majority of patients where the tumour had already metastasised by the time of diagnosis, the situation was even worse: 15% survived six months, 5% lived for one year, and none

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survived beyond two and a half years.⁵ The situation has not changed significantly since then. The overall five year survival for pancreatic cancer in Quebec (1984–1986) was 6% for men and 7% for women.⁶

Risk factors

EPIDEMIOLOGICAL STUDIES OF PANCREATIC ADENOCARCINOMA

There have been a number of international epidemiological studies investigating dietary aspects of pancreatic cancer risk. Descriptive studies have shown strong positive correlations between per capita consumption of oil, fat, butter, beef, pork, sugar, and eggs as risk factors and fruits, vegetables, and whole grain bread as protective factors.⁷ Case-control studies, using the same questionnaire in four countries in three continents, have shown that there is a strong positive association with carbohydrate and cholesterol intake, and a strong negative correlation with dietary fibre intake. Cigarette smoking, but not coffee or alcohol consumption, appears to be a consistent risk factor.⁸ A new finding from the Montreal group was the very strong relationship between dietary salt intake and pancreatic cancer risk (salt in cooking: relative risk (RR) 3.81, $p=0.009$, table salt: RR 4.28, $p=0.0001$). Consumption of smoked food also appeared to be a significant risk factor for pancreatic cancer.⁹

An interesting observation was made from studying American women who served as nurses in Vietnam during the Vietnam war. They had a significantly increased risk of pancreatic cancer compared with non-Vietnam nurses (RR 5.74) and women in the US population (standardised mortality ratio = 2.78, 95% CI 1.11–5.73).¹⁰ It is difficult to interpret this result since little is known about the lifestyle of these women aside from their professional activities during the war. Although these women were not directly involved in combat during the war, they may have been exposed to a number of potentially dangerous chemicals. An increase in the incidence of cancer was also observed in male Vietnam veterans; however, a statistically significant excess of pancreatic cancer was only reported in one study.¹¹ Black Vietnam veterans from Michigan had a proportional mortality ratio of 9.09 (95% CI 2.93–21.22) for pancreatic cancer as compared with non-Vietnam Michigan veterans. Among persons working with such chemicals as beta-naphthylamine and benzidine, the mortality rate for cancer of the pancreas is increased fivefold.¹² Other epidemiological studies have shown several occupations to be associated with increased RRs for pancreatic cancer, but the numbers of people in each group were small, and although the point estimates were large, the confidence intervals were very wide.¹³

PREVIOUS MEDICAL HISTORY AND PANCREATIC ADENOCARCINOMA

A previous history of pancreatitis is a risk factor for subsequent pancreatic adenocarcinoma. The strength of this association is uncertain,

but a recent case-control study of 2639 patients with pancreatic cancer showed that a history of pancreatitis seven years or more before cancer diagnosis was associated with a RR for pancreatic cancer of 2.04 (95% CI 1.53–2.72). This effect is unlikely to be the result of misclassification bias. The risk was not significantly different for chronic or acute pancreatitis and was not affected by adjustment for potentially confounding variables.¹⁴ Another result which supports this finding comes from a multicentre historical cohort study of 2015 chronic pancreatitis patients from six countries.¹⁵ During a mean follow up period of 7.4 years, 56 cancers were found in this group. Based on country specific incidence data, this results in a standardised incidence ratio of 26.3 (95% CI 19.9–34.2). Standardised incidence ratios for patients with a minimum of two and five years of follow up were 16.5 (95% CI 11.1–23.7) and 14.4 (95% CI 8.5–22.8), respectively.

Diabetes mellitus has long been associated with pancreatic cancer. Recently, Evans *et al*¹⁶ reported a large pedigree with nine cases of pancreatic cancer inherited in an autosomal dominant fashion over three generations. All family members diagnosed with pancreatic cancer also developed diabetes and exocrine insufficiency. Of these, five had diabetes for more than 10 years before diagnosis of the cancer while the remaining cancers were diagnosed concomitantly with the diabetes. There has been some uncertainty as to whether diabetes in the majority of pancreatic cancer patients is a cause or a symptom of the tumour, and the relationship between the two diseases is particularly difficult to determine when diabetes is diagnosed around the same time as the cancer. Some of these uncertainties were resolved by a recent meta-analysis of 20 case-control and cohort studies of diabetes and pancreatic cancer¹⁷; an overall RR of 2.1 (95% CI 1.6–2.8) of pancreatic cancer associated with a history of diabetes mellitus was determined. In all the studies analysed, duration of diabetes of five years or more resulted in the same RR for pancreatic cancer as for shorter durations of diabetes. This meta-analysis shows that there probably is a true aetiological relationship between the two diseases. Interestingly, in the two studies where a distinction between non-insulin and insulin dependent diabetes was made, all the cases of pancreatic cancer were seen in those with non-insulin dependent diabetes.

Contrary to earlier data,¹⁸ a previous cholecystectomy does not appear to be a risk factor for pancreatic cancer.¹⁹ An increased risk of cancer may be associated with cystic fibrosis (CF). The short life span of CF patients makes this difficult to confirm; however, there have been several reports of cancer in patients with CF. The most common cancer among these patients is leukaemia. However, three cases of pancreatic cancer (ages at diagnosis: 23, 22, and 42 years) have been reported.²⁰

There is some evidence that a previous partial gastrectomy is a risk factor for pancreatic cancer. Firstly, of 779 men who underwent peptic ulcer surgery, 11 died of carcinoma of the

pancreas; 3.9 cases of pancreatic cancer were predicted to occur in this cohort.²¹ A second study of 4235 post-gastrectomy patients showed a RR of 3.2 for pancreatic malignancy associated with previous gastric surgery.²² Thirdly, an assessment of the risk factors for pancreatic cancer showed a RR of 5.3 (95% CI 1.6–21.5) associated with gastrectomy.²³ For those directly interviewed, the risk was high but not significant. Finally, a threefold increased risk for pancreatic adenocarcinoma was determined after investigating 180 cases with the disease, nine of whom had undergone partial gastrectomy.²⁴ This increased risk may be related to gastric hypoacidity leading to increased production of such carcinogens as *N*-nitroso compounds in gastric juice.^{22,23} Possibly of relevance is that there may be a risk of pancreatic cancer associated with blood group A. In one study of 620 patients with carcinoma of the pancreas, there was a non-significant RR of 1.25 for pancreatic cancer associated with blood group A (compared with blood group O). Blood group A is strongly associated with an increased risk of stomach cancer.²⁵

Familial and genetic risk factors for pancreatic adenocarcinoma

Pancreatic adenocarcinoma has not been regarded as a disease in which inheritance plays an important role. However, new data suggest that clearly genetic factors may be important in a minority of cases.

EPIDEMIOLOGICAL STUDIES

A study of 362 cases of pancreatic adenocarcinoma and 1408 hospital controls from northern Italy showed an adjusted RR of 2.8 (95% CI 1.3–6.3) for pancreatic adenocarcinoma in association with a family history of this cancer in first degree relatives.²⁶ In francophone Montrealers, 7.8% of cases but only 0.6% of controls reported a family history of pancreatic cancer.²⁷ Further questioning of people with familial pancreatic adenocarcinoma did not indicate any environmental exposure differences between the cases and matched controls. An increased risk for pancreatic cancer was also reported for people with a close relative with any cancer (OR 1.86, 95% CI 1.42–2.44).²⁸ Persons with close relatives with pancreatic cancer had an even higher risk (OR 5.25, 95% CI 2.08–13.21). A population based study of familial cancer based on the Utah Population Database found a familial RR of 1.25 for pancreatic cancer.²⁹ However, this increased risk was not significant.

CASE SERIES

Several case series of families with three or more affected members support the hypothesis that genetic factors are an important determinant of risk. These are listed in table 1. Of particular note is the large number of families reported by Lynch. First, in 1990, he described 18 families in which a total of 47 people were

diagnosed with the disease (table 1, families 24–40).³⁰ In 1994, he presented a family with four cases of histologically verified pancreatic cancer through three generations.³¹ The mean age at diagnosis was 68.5 years. Cancer of the prostate, mouth, colon, lung, and breast, as well as lymphoma, were also found in this kindred (table 1, family 41). Finally, in 1995, he described eight pancreatic cancer prone families (table 1, families 42–49).³² There were 25 cases in total in the eight families; the mean age at diagnosis was 62.8 years (median 60, range 45–90). In half the families, the disease was present in two consecutive generations; the pattern of cancer occurrence in these families appears to be consistent with an autosomal dominant mode of inheritance. One of these families is noteworthy (table 1, family 48). There is a total of four cases of pancreatic cancer over two generations. In the older generation, both sibs died of the disease; in the younger generation, four of the seven sibs have been diagnosed with cancer of the breast, ovary, lung, or pancreas. A fifth sib had double primary cancer of the breast (at the age of 39) and pancreas (at the age of 59). This is suggestive of a BRCA1 or BRCA2 related pattern of disease (discussed below).

Inherited syndromes in which pancreatic cancer is a feature (table 2)

SYNDROMES WHERE CANCER IS THE DOMINANT FEATURE

Familial atypical mole-multiple melanoma

Pancreatic adenocarcinoma is probably the second commonest cancer in familial atypical mole-multiple melanoma (FAMMM) families (table 3). The observed/expected (O/E) ratio for the frequency of pancreatic cancer among 200 members of nine FAMMM families was 13.4 ($p < 0.001$).³³ In several chromosome 9p linked FAMMM families, a mutation in the cell cycle inhibitor gene p16^{INK4A} has been found to cosegregate with both melanoma and pancreatic adenocarcinoma.^{34–36} In some families, most persons with cancer have pancreatic or other gastrointestinal malignancies rather than melanoma.³⁷

This excess of pancreatic cancer in FAMMM families may be attributed, in part, to ascertainment bias. Investigations of the tumour spectrum of the FAMMM syndrome showed no excess of pancreatic tumours in a total of 15 FAMMM kindreds and 370 people diagnosed with melanoma.^{38–40} However, there may be a biological explanation for the subset of FAMMM kindreds who have an excess of pancreatic cancer. In families where the p16^{INK4A} mutation impairs the function of its corresponding protein in *in vitro* assays, the risk of pancreatic cancer was increased thirteen-fold (standardised incidence ratio: 13.1, 95% CI 1.5–47.4), whereas no cases of pancreatic cancer were found in families with p16^{INK4A} mutations that did not affect the function of the protein in the assay used by this group.³⁵ In the study of Whelan *et al*,³⁷ a Gly93Trp missense mutation in p16^{INK4A} was found in all

Table 1 Familial pancreatic cancer: case reports*

Family No	No of subjects reported in pedigree	No of pancreatic cancer cases (No of affected generations)	Other cancers (No of cases if >1)	Ref
1	19	4 (1)	None	108
2	38	4 (1)	Cervix, prostate, colon, double primary of rectum and prostate	109
3	2	2 (2)	Not reported	110
4	7	3 (1)	None	111
5	42	4 (2)	Breast, colon	112
6	35	3 (3)	Stomach (2), urinary bladder, colon (6), endometrium, lung, neuroblastoma	55
7	5	3 (1)	Colon, stomach	113
8	3	3 (3)	Not reported	114
9	23	3 (1)	Breast, lung, uterus	115
10	29	2 (1)	Bladder, Hodgkin's, breast	27
11	19	2 (1)	None	27
12	9	2 (1)	Leukaemia	27
13	22	3 (1)	Breast, lung, cervix	27
14	19	2 (1)	Mouth (double primary with pancreas), colon, penis, breast (2), reticulosarcoma	27
15	13	2 (1)	None	27
16	10	2 (1)	None	27
17	19	3 (1)	None	27
18	16	2 (2)	Unknown site, colon, skin	27
19	11	3 (2)	Breast, colon	27
20	14	2 (2)	None	27
21	8	2 (2)	None	27
22	17	2 (2)	Uterus (2), prostate, lung, breast	27
23	17	2 (2)	Stomach, breast, lung (2)	27
24	6	3 (2)	Breast, lymphoma	30
25	5	2 (1)	Prostate, lip	30
26	16	3 (2)	Breast (2), endometrium	30
27	24	2 (1)	Endometrium, colon (2), multiple myeloma	30
28	7	2 (2)	Leukaemia, colon, breast, ovary	30
29	12	2 (1)	None	30
30	16	4 (1)	Lung	30
31	5	2 (1)	Breast (double primary with pancreas)	30
32	22	3 (1)	Breast (3)	30
33	16	3 (2)	Lung (2), ampulla of Vater, breast	30
34	18	3 (1)	Melanoma	30
35	10	4 (2)	Breast, caecum	30
36	11	2 (1)	Prostate (2), breast (3)	30
37	11	2 (2)	Malignant melanoma, primary site unknown (2), breast (2)	30
38	17	3 (2)	Lung (2), breast, colon (5)	30
39	18	3 (1)	Colon (4), stomach, pelvis, testis, bronchiogenic carcinoma, lung, breast, leukaemia	30
40	8	2 (1)	Bile duct, breast	30
41	57	4 (3)	Prostate, mouth, colon, lung, breast, lymphoma	31
42	43	6 (2)	Prostate, lung, gallbladder, breast	32
43	69	3 (2)	Colon (2, 1 double primary), prostate, tongue	32
44	21	3 (1)	Abdominal	32
45	53	3 (1)	Colon, cutaneous malignant melanoma, lung, thyroid	32
46	14	2 (2)	Melanoma	32
47	68	2 (1)	Ampulla of Vater, submandibular gland, testicle (double primary), cervix, neuroblastoma	32
48	41	4 (2)	Breast (2, 1 double primary of pancreas and breast), ovary, lung	32
49	83	2 (2)	Gallbladder, oesophagus, lung (2), kidney, lymphoma, triple primary of leukaemia, brain, breast	32

* Defined as two or more cases of pancreatic cancer.

affected family members. This mutation affects the function of the p16^{INK4A} protein in vitro, and is associated with increased cancer risk.⁴¹

Familial breast and ovarian cancer syndromes

Hereditary breast cancer can be site specific, but in many families other cancers are seen in those who have inherited the at risk haplotype. Ovarian cancer is seen in excess in most BRCA1 linked families. For BRCA2 families, male breast cancer appears to be a defining feature.⁴² In addition, pancreatic adenocarcinoma is seen in some breast cancer families accounted for by BRCA1 and BRCA2 mutations (fig 1).^{43,44} In these families, persons with pancreatic cancer have inherited the at risk haplotype and therefore it is likely that the pancreatic adenocarcinoma seen in these people is accounted for by BRCA1 (fig 1A) or BRCA2 (fig 1B-D) mutations. Johannsson *et al*⁴⁵ investigated 15 Swedish kindreds with BRCA1 mutations and found two cases of pancreatic cancer (diagnosed at ages 54 and 42). Both cases had inherited the at risk haplotype. Four out of seven families with known BRCA2 mutations have at least one case of pancreatic cancer (fig 1B-D).⁴² Three out of seven breast cancer

pedigrees from Iceland contain one or more cases of pancreatic or biliary tract cancer.⁴⁶ All the cases of pancreatic cancer were men. Most, if not all, Icelandic breast cancer families can be accounted for by a founder mutation in BRCA2.⁴⁷ Additionally, studying the whole population of Iceland, Tulinius *et al*⁴⁸ noted a significant excess (RR 1.66) of pancreatic cancer in the male first degree relatives of women with breast cancer. The point estimate for female relatives was also raised but was not significant at the 5% level. A weighted estimate for all degrees of relatedness also gave a significant result for males only (RR 1.30, p<0.05). The risk for male first degree relatives was greater if the proband was diagnosed with breast cancer at less than 45 years of age rather than 45 years or older (2.16 *v* 1.49), but this was not so for female first degree relatives (0.59 *v* 1.67). An assessment of the impact of family history on ovarian cancer risk used the Utah Population Data Base, linked to one million people in the Utah Cancer Registry, to study 662 cases and 2647 controls.⁴⁹ A family history of pancreatic cancer was estimated to account for 4.8% of ovarian cancer cases (95% CI 1.7-7.8). This risk may be attributed to mutations in BRCA1 or BRCA2. Although these combined data are

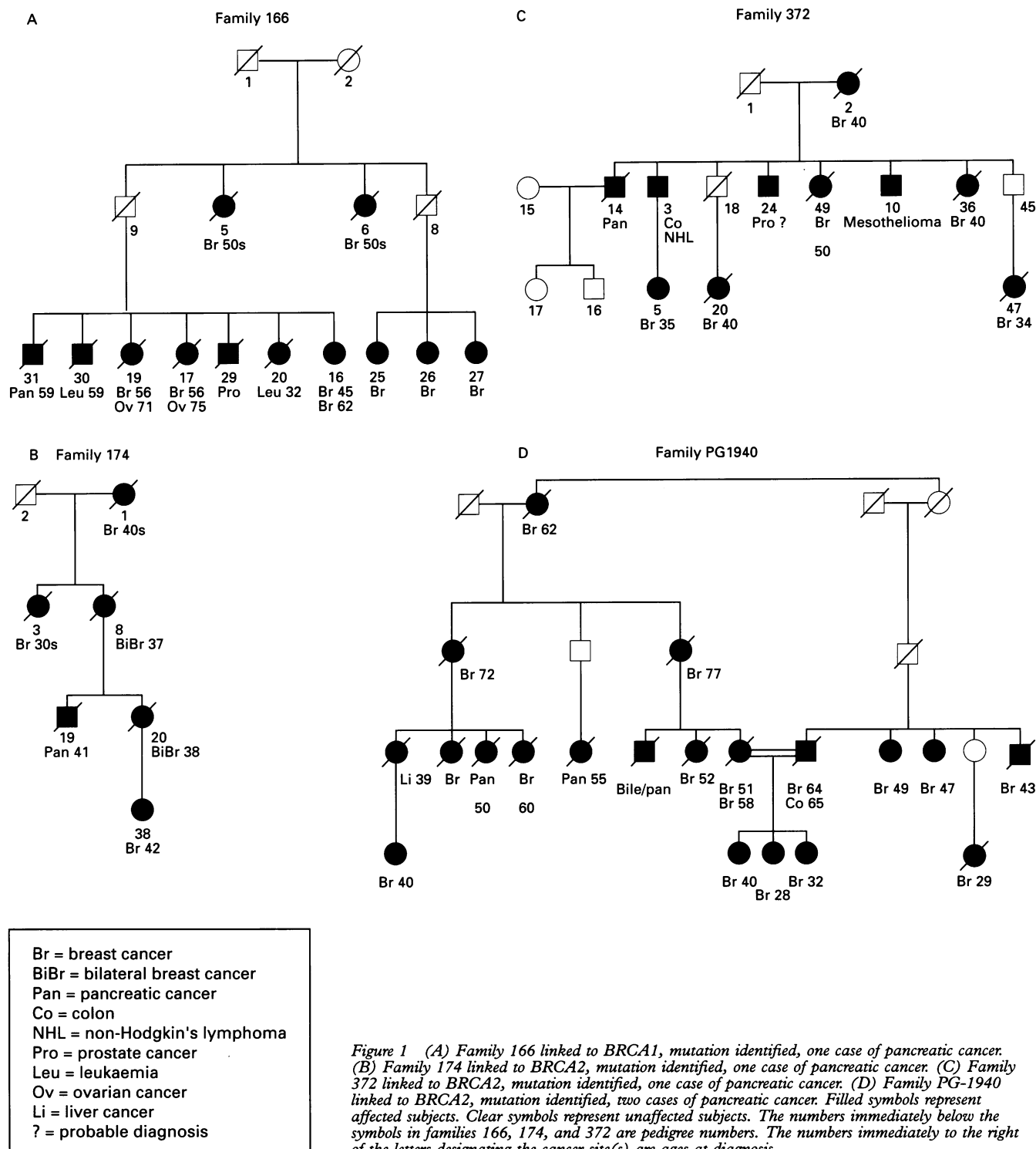


Figure 1 (A) Family 166 linked to BRCA1, mutation identified, one case of pancreatic cancer. (B) Family 174 linked to BRCA2, mutation identified, one case of pancreatic cancer. (C) Family 372 linked to BRCA2, mutation identified, one case of pancreatic cancer. (D) Family PG-1940 linked to BRCA2, mutation identified, two cases of pancreatic cancer. Filled symbols represent affected subjects. Clear symbols represent unaffected subjects. The numbers immediately below the symbols in families 166, 174, and 372 are pedigree numbers. The numbers immediately below the letters designating the cancer site(s) are ages at diagnosis.

very suggestive of a role for BRCA2 and probably also BRCA1 in pancreatic carcinogenesis, further studies on the tumours themselves will be required.

Hereditary non-polyposis colorectal cancer

Pancreatic cancer is included in the tumour spectrum of hereditary non-polyposis colorectal cancer (HNPCC), but it is not certain whether the excess number of cases seen is a chance finding, possibly related to ascertainment biases.⁵⁰ In a study of 40 Finnish HNPCC kindreds, six of 293 putative gene

carriers with clinically or histologically documented cancer had pancreatic carcinoma.⁵¹ The cumulative risk for biliary tract cancer, including pancreatic cancer, by the age of 80, was 17.5%. Conversely, an investigation of 22 Dutch HNPCC families identified no cases of pancreatic cancer among 148 cancer patients.⁵² Lynch *et al*^{53,54} have described a number of HNPCC kindreds with at least one person diagnosed with pancreatic cancer. In the most notable of these (table 1, family 6), one case of pancreatic cancer was seen in three of the five affected generations.⁵⁵ The average age at diagnosis of this tumour in the family was 56.3 years.

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome patients have hamartomatous gastrointestinal polyps and pigmented maculas involving skin and mucous membranes, inherited in an autosomal dominant fashion. In 1986, Bowlby⁵⁶ described a 15 year old male with Peutz-Jeghers syndrome who died of pancreatic adenocarcinoma. In the "Harrisburg family", one of the original Peutz-Jeghers families described in 1949, one man died of pancreatic adenocarcinoma at the age of 69.⁵⁷ Of 31 Peutz-Jeghers patients from 13 unrelated kindreds, 15 (48%) developed cancer; four had adenocarcinoma of the pancreas.⁵⁸ In another study, 16 (22%) of 72 Peutz-Jeghers patients developed cancer⁵⁹; of these, there was one case of pancreatic cancer.

Li-Fraumeni syndrome

Li-Fraumeni syndrome is an autosomal dominantly inherited predisposition to early onset sarcoma, breast cancer, and other neoplasms, including brain tumours, leukaemia, and lung cancer. Adenocarcinoma of the pancreas may also be included in the tumour spectrum of this syndrome.⁶⁰ In a study of 24 Li-Fraumeni kindreds, one case of pancreatic cancer was seen in each of three families and two cases were seen in a fourth.⁶¹

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP) is characterised by the presence of hundreds of colorectal adenomas which often progress to carcinomas. The disease, which is inherited in an autosomal dominant fashion, is also associated with a number of benign and malignant extracolonic lesions, including, rarely, cancer of the pancreas. A study of 197 FAP pedigrees found a RR of 4.46 (95% CI 1.2–11.4) for pancreatic adenocarcinoma in patients with the syndrome.⁶²

Ataxia telangiectasia

Ataxia telangiectasia (AT) is a recessively inherited syndrome characterised by progressive cerebellar ataxia, telangiectasias, increased susceptibility to sinopulmonary infections, oculomotor apraxia, and risk of lymphoproliferative malignancies. The recently described AT gene, ATM, maps to chromosome 11q22–23.⁶³ There is an increase in the incidence of cancer in homozygotes and probably in heterozygotes as well.⁶⁴ A number of studies investigating the

incidence of cancer in the relatives of patients with AT report an association of pancreatic adenocarcinoma with the syndrome. There is a report of a 19 year old female AT patient with dysgerminoma of the right ovary, papillary carcinoma of the thyroid, and adenocarcinoma of the pancreas.⁶⁵ Among close relatives in 25 families with AT probands, there were seven cases of pancreatic cancer; 1.4 cases were expected ($p < 0.02$).⁶⁶ In a study of 110 white families with AT, seven cases of pancreatic cancer were observed in blood relatives of AT patients (3.3 cases were expected). Among the spouse controls, only one case was observed (1.3 were expected).⁶⁷ Another study found no cases of pancreatic cancer in AT patients or their parents but two in grandparents, representing a proportional mortality ratio of 2.78.⁶⁸ Neither of the latter two studies reported the statistical significance of the data.

OTHER SYNDROMES

Williams syndrome

Cancer of the pancreas has been observed in a case of Williams syndrome, an autosomal dominant condition^{69,70} characterised by unusual facial features, congenital abnormalities, mental retardation, and infantile hypercalcaemia.⁷¹ The pancreatic cancer seen in this patient may be related to the hypercalcaemia.⁷²

Hereditary pancreatitis

Two cases of pancreatic cancer were reported in one family with hereditary pancreatitis (HP).⁷³ Kattwinkel *et al*⁷⁴ described another HP kindred in which there was one case of pancreatic cancer. However, in the two other HP families reported in the same paper, there were no confirmed cases of pancreatic malignancy. It is, therefore, unclear whether or not there is a genetic relationship between the two diseases. The gene for at least some forms of hereditary pancreatitis maps to chromosome 7q.^{74A}

Somatic alterations in pancreatic adenocarcinoma

A number of proto-oncogenes and tumour suppressor genes are reported to be frequently mutated in pancreatic adenocarcinoma. Abnormal expression of adhesion molecules has also been reported.

Table 2 Inherited syndromes in which pancreatic adenocarcinoma is featured

Syndrome	Gene(s) (locus)
FAMMM (familial atypical mole-malignant melanoma)	p16 (9p21)
Peutz-Jeghers	Not known
Li-Fraumeni	TP53 (17p13.1)
HNPCC (hereditary non-polyposis colorectal cancer)	hMSH2 (2p15–16)
	hMLH1 (3p21–22)
	hPMS1 (2p31–33)
	hPMS2 (7p21)
FAP (familial adenomatous polyposis)	APC (5q12–21)
Ataxia telangiectasia	ATM (11q22–23)
Hereditary pancreatitis	HPG (7q33-qter)
Williams	7q11.23
	?4p33–35.1 (in a minority)

Table 3 FAMMM families with pancreatic cancer

No of subjects in pedigree	No of melanomas (No of affected generations)	No of pancreatic cancers (No of affected generations)	Other cancers (No of cases if >1)	Ref
12	4 (2)	2 (1)	Cervix, breast, bone sarcoma	116
34	3 (2)	1	Stomach (2), lung (3), lymphoma, ovarian (double primary with pancreas)	117
61	8 (2)	4 (1)	Bronchus, childhood cancer (2), nasopharynx, breast, tongue, larynx, primary site unknown	33
175	8 (2)	6 (1)	Liver, parotid, stomach, oesophagus, leukaemia, lung, breast (2), prostate, uterus, cervix, nasopharynx, (there was one case of double primary of pancreas with melanoma)	33
36	4 (1)	1	Liver, primary site unknown (probably digestive tract), breast (double primary with melanoma), kidney	33
22	6 (2)	3 (2)	Endometrium	118
10	2 (2)	3 (2)	Breast, tongue (there was one case of double primary of pancreas with melanoma)	37
23	4 (3)	4 (3)	Not reported	119

Table 4 Codon 12 K-RAS mutations in pancreatic cancer

No of cases analysed	No of cases with codon 12 K-RAS mutation (%)	Ref
22	21 (95)	77
30	28 (93)	120
63	47 (75)	78
8	7 (88)	99
82	68 (83)	121
7	6 (86)	96
35	25 (71)	80

ONCOGENES

The K-RAS proto-oncogene encodes a protein involved in cell growth and differentiation.⁷⁵ K-RAS mutations have been found in numerous human neoplasms.⁷⁶ An activating mutation in codon 12 of this gene was detected in 21 (95%) of 22 formalin fixed, paraffin embedded carcinomas of the exocrine pancreas.⁷⁷ Normal tissue from these patients contained no K-RAS mutations. It is probable that mutation of this gene is a critical event in oncogenesis of most human carcinomas of the exocrine pancreas, and data from six additional studies support this conclusion (table 4).

Interestingly, two distinct K-RAS mutations were found in a small number of patients.⁷⁸⁻⁸⁰ It is not always possible to determine whether these two mutations are found within the same cell or in two distinct areas of the tumour. However, in studies where this information is available, it appears that there were two subpopulations of tumour cells, each carrying a different mutation.

TUMOUR SUPPRESSOR GENES

p16^{INK4A} is frequently homozygously deleted in cell lines derived from a number of tumour types.⁸¹⁻⁸³ In melanoma cell lines where one copy of the gene is absent, the remaining copy is frequently mutated.⁸⁴ In one study, allelic deletions of this gene were found in 22 (85%) of 26 pancreatic adenocarcinomas.⁸⁵

There have been few reports of point mutations in p16^{INK4A}. This may be accounted for by two pieces of data: firstly, the gene can be inactivated by methylation of the CpG island 5' of the coding region.⁸⁶ 5' CpG islands of seven of nine non-small cell lung cancer cell lines with no known homozygous deletions were found to be fully methylated. None of these cell lines expressed p16^{INK4A}, whereas all unmethylated cell lines analysed expressed p16^{INK4A}. Secondly, the gene can have micro-

deletions only detectable using an array of microsatellites close to the gene. These were confirmed by fluorescent in situ hybridisation (FISH): in nine primary tumours analysed, FISH identified eight cases of homozygous deletion and one case of hemizygous deletion. Many of these deletions spanned less than 200 kilobases.⁸³

Increased expression of TP53 was observed in nine of 12 pancreatic cancer cell lines. Of these nine cell lines, seven were found to have point mutations in TP53. When six primary tumours overexpressing TP53 were investigated, four displayed both mutations in TP53 and loss of expression of tumour suppressor gene, Deleted in Colon Cancer (DCC).⁸⁷ Pellegata *et al*⁸⁰ studied TP53 and K-RAS together. They detected mainly missense mutations in TP53 in 18 (51.4%) of 35 ductal tumours studied but found no gene alterations in six exocrine non-ductal tumours and only one TP53 mutation in 12 endocrine tumours. They conclude that aberrant K-RAS and TP53 genes cooperate in tumorigenesis in pancreatic ductal carcinomas. These data suggest that the multi-hit model for carcinogenesis⁸⁸ applies to cancer of the pancreas.

Somatic mutations of another tumour suppressor gene, APC, which is responsible for familial adenomatous polyposis (FAP), were detected in four of 10 pancreatic cancers.⁸⁹ There is an increased risk of pancreatic cancer in FAP⁶² (see above).

HOMOZYGOUS DELETIONS

Homozygous germline deletions are very uncommon, probably because of lethality during embryonic development. In tumour tissue, where there are less constraints, they are more common. Their presence has aided the discovery of tumour suppressor genes. Thus the isolation of tumour suppressor genes RB1, DCC, and p16^{INK4A} was made easier by the presence of homozygous deletions in tumour tissue.^{84 90 91} In pancreatic neoplasms, this genetic alteration has been reported at three loci: 13q, 9p, and 18q.

Using the powerful representational difference analysis (RDA) technique,⁹² Schutte *et al*⁹³ discovered two clones that were present only in the germline of a patient with pancreatic cancer. Intriguingly, both these clones, named Deleted in Pancreatic Cancer locus 1 (DPC1) and DPC2, mapped to a region of chromosome

13q that lay within the smallest linked region of BRCA2. The patient was an 84 year old woman with localised pancreatic adenocarcinoma. There was a strong family history of adenocarcinoma, mainly at an advanced age. Although there was no suggestion of a germline mutation in BRCA2 in this family, the position of this homozygous deletion was a significant help in the search for BRCA2, which was cloned less than six months after the paper was published. It is now known that BRCA2 lies completely within this deletion.⁹⁴ Thus both somatic and germline mutations in BRCA2 are important in adenocarcinoma of the pancreas.

p16^{INK4A} was homozygously deleted in five of 10 cell lines and 10 of 27 xenografts of pancreatic carcinomas.⁸⁵ This gene deletion corresponds to DPC3 in the terminology of Hahn *et al.*⁹⁵ Homozygous deletions of the gene were also seen in cell lines derived from a number of other cancers.^{82,83} As for BRCA2, it appears that p16^{INK4A} is important both in inherited and non-inherited forms of pancreatic adenocarcinoma.

A span in the 18q21.1 region, designated DPC4, was homozygously deleted in 25 (30%) of 84 pancreatic carcinomas.⁹⁵ Allelotypes of pancreatic adenocarcinoma identify chromosome 18q as having a high frequency of allelic loss.^{96,97} Since this chromosome region also contains the DCC gene locus, it is relevant to ask whether DCC or DPC4 or both, are involved in the development of this human malignancy. There are data documenting a reduction or complete loss of DCC expression in half of primary pancreatic tumours and in most cell lines analysed. Furthermore, allelotype data show that loss of heterozygosity (LOH) at 18q spans the entire DCC gene area.⁹⁷ However, analysis of four homozygous deletion cases using multiple sequence tagged site markers within or flanking the DCC gene showed that none of the four cases involved the DCC gene.^{95,98}

ALLELOTYPED STUDIES

An allelotype of seven pancreatic adenocarcinoma was carried out to determine the pattern of allelic loss associated with this neoplasm.⁹⁶ Chromosome arms 3p, 4q, 7p, 10p, 11q, 12q, 16q, 17p, and 18q showed allelic loss. All four of the cases with 17p deletions had TP53 mutations. In contrast to the data of Horii *et al.*,⁸⁹ no loss of 5q (the APC locus) was observed in these seven tumours. The fractional allelic loss (FAL) was 0.18. FAL is defined as the average frequency of LOH at all loci for which allelic markers were informative in the patient's normal cells. The extent of FAL was associated with prognosis: patients with lower FAL values survived longer than did those with more extensive accumulated genetic damage. Another allelotype of pancreatic adenocarcinoma using xenograft enrichment identified a high frequency of LOH at 1p (67% LOH), 9p (89% LOH), 17p (100% LOH), and 18q (89% LOH).⁹⁷ In all cases LOH at 17p involved markers near the TP53 locus.

LOH at 18q spanned the entire DCC area, but it is likely that the recently described DPC4 gene is the target for this region of LOH. The FAL was 0.36; this higher figure is probably because of the xenograft enrichment, as pancreatic cancer is often accompanied by a marked host desmoplastic reaction. The LOH on chromosomes 9p, 17p, and 18q can probably be accounted for by p16^{INK4A}, TP53, and DPC4, respectively, but it is likely that other genes of relevance to pancreatic adenocarcinoma remain to be uncovered.

ADHESION PROTEINS

Complete loss of DCC expression was observed in four of six primary pancreatic carcinomas,⁸⁷ eight of 11 pancreatic carcinoma cell lines, and four of eight primary ductal adenocarcinoma of the pancreas.⁹⁹ Interestingly, undifferentiated tumours were found to have reduced or absent DCC expression, while DCC expression was conserved in more differentiated tumours. It may be concluded that the loss of DCC expression probably plays a role in pancreatic tumourigenesis, especially of differentiated tumours. This may be related to the fact that the DCC protein product displays homology to neural cell adhesion molecule N-CAM.¹⁰⁰⁻¹⁰² The relationship between expression of DCC and the nearby DPC4 has not yet been fully investigated.

Another adhesion molecule involved in pancreatic adenocarcinoma is the cell surface glycoprotein, CD44, which mediates cell-cell adhesion. The level of CD44 expression in human pancreatic adenocarcinoma cells is over one hundred times higher than the level in normal pancreatic cells.¹⁰³ Since CD44 has been shown to be involved in metastasis and cancer cell invasion,^{104,105} and anti-CD44 antibody suppressed *in vitro* pancreatic cancer cell invasion to a matrigel basement membrane,¹⁰⁶ it may be concluded that CD44 is a major factor in pancreatic adenocarcinoma cell invasion. This finding may have implications not only for differential diagnosis of this malignancy, but possibly for treatment strategies.

Screening

Information on somatic gene mutations is potentially useful for diagnosis of pancreatic cancer. Convincingly, K-RAS mutations have been detected in DNA purified from pancreatic juice, peripheral blood, and stool of patients with the disease.^{79,106A} K-RAS mutations in stool samples from nine patients were identical to mutations found in the corresponding primary tumour.^{106A} This in an important direction for research since early diagnosis of this cancer is probably the best way to improve prognosis. However, how broadly applicable these findings are at the moment is questionable.

The US Preventive Services Task Force does not recommend routine screening of asymptomatic persons for pancreatic adenocarcinoma.¹⁰⁷ As yet, there is no evidence indicating that screening would be worthwhile

for people with a family history of cancer that might place them at increased risk.

Conclusion

Adenocarcinoma of the pancreas is a difficult disease to diagnose and treat. Prognosis is poor. However, knowledge gained from the study of rare, hereditary forms of the disease may prove extremely useful in understanding its aetiology. Somatic genetic changes that accompany the development of this tumour may provide a means for earlier diagnosis and possibly new treatment methods.

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