

1

Epidemiology and genetics of pancreatic cancer

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Introduction

Pancreatic ductal adenocarcinoma (and its histological variants), also referred to as pancreatic cancer (PC) comprises 90% of exocrine pancreatic neoplasms [1]. This highly aggressive cancer is the fourth leading cause of cancer death in the USA [2]. More than 80% of patients with PC present with advanced disease that is incurable by surgery. Most tumors greater than 5 cm in size show disseminated metastases at presentation [3]. The 5-year survival rate of advanced PC is poor (<5%) with a median survival of <6 months. The 5-year survival rate improves to 20–30% in patients who harbor small, early invasive cancers (usually <3 cm) and are candidates for surgical resection [2]. Thus, early diagnosis of PC before frank invasion occurs is critical to improve patient outcomes.

Mucinous cystic neoplasms (MCNs) are mucin-secreting, cystic neoplasms of characteristic histopathology and variable clinico-biological profiles. They comprise 10–45% of cystic pancreatic neoplasms [4]. Intraductal papillary mucinous neoplasms (IPMNs) are characterized by cystic dilatation of ducts and intraductal papillary tumors with variable mucin production and tumor histobiology. Intraductal papillary mucinous neoplasms constitute 15–25% of cystic pancreatic neoplasms and typically show slow intra-luminal growth and low metastatic potential [4, 5]. Subsets of these two mucinous tumors progress to PC.

Pancreatic cancer

Epidemiology

Pancreatic cancer is one of the most lethal cancers, characterized by invasive growth and rapid dissemination despite a relatively well-differentiated histomorphology [3]. In the USA, PC contributed to 32 300 estimated deaths in 2006 of an estimated

2 Pancreatic Cancer

33 730 new pancreatic cancer cases [6]. Eighty percent of PC manifest clinically in patients aged 60–80 years; only about 10% of patients are below the age of 50 years [7]. Pancreatic cancer is found more commonly in men. Predisposing risk factors include cigarette smoking, chronic pancreatitis, exposure to radiation and chemicals, diabetes mellitus and hereditary cancer syndromes [7].

Smoking is by far the most important risk factor accounting for approximately 25% of PCs [7]. Smokers show a two-fold increased risk for PC compared with non-smokers. Chronic pancreatitis is a well-documented risk factor for PC [7, 8]. It is postulated that high cell turnover associated with chronic pancreatitis (either acquired or hereditary) predisposes to PC especially in the setting of defective DNA repair mechanisms [7]. It is interesting to note that KRAS and p16 mutations seen with PC are also observed in patients with chronic pancreatitis [9, 10]. In addition to the above risk factors, microscopic and macroscopic precursors of PC have been identified.

Microscopic precursors of pancreatic cancer

It is now established that invasive PCs originate from microscopic, non-invasive neoplastic epithelial proliferations referred to as pancreatic intra-epithelial neoplasias (PanINs) [2, 11]. The PanINs develop in small-caliber pancreatic ducts (usually < 5 mm in diameter) and are histologically classified into three types, PanINs-1, 2 and 3 [12]. The histological spectrum of PanINs is summarized in Table 1.1. These microscopic ductal epithelial growths show histogenetic progression from low-grade PanIN (PanIN-1 to PanIN-2) through high-grade PanIN (PanIN-3) to PC analogous to the adenoma–carcinoma sequence in colorectal cancers [2]. The tumor progression is thought to occur through a series of sequential, polychromosomal genetic mutations [11, 13]. Early, intermediate and late genetic events of progression of PanINs to PC include KRAS activation, inactivation of the p16/CDKN2A tumor suppressor gene and the loss-of-function mutations of TP53 and DPC4/SMAD4 tumor suppressor genes respectively (Figure 1.1) [2].

Macroscopic precursors of pancreatic cancer

Intraductal papillary mucinous neoplasms

Intraductal papillary mucinous neoplasms (IPMNs) are characterized by predominant intraductal growth, papillary epithelial configuration, mucin overproduction and variable histobiologic profiles [14]. Peak age of incidence is in the 7th and 8th decades. Men are more commonly affected. Most patients manifest abdominal pain,

Table 1.1. Histological spectrum of pancreatic intraepithelial neoplasias (PanINs) [2,12]

Lesion type	Histological grade	Histological characteristics	Genetic pathways involved
PanIN-1	Low grade	Flat, micropapillary or papillary epithelial lesions composed of tall columnar cells. Minimal degree of atypia	KRAS activation
PanIN-2	Intermediate grade	Mostly papillary epithelial lesions with some nuclear abnormalities and rare mitoses. Moderate degree of atypia	Inactivation of the p16 tumor suppressor gene
PanIN-3	High grade	“Carcinoma-in-situ”; Papillary, micropapillary epithelial growths with cytonuclear abnormalities resembling non-invasive carcinoma (No basement membrane invasion)	Inactivation of the *TP53 and *DPC4 tumor suppressor genes

*TP53: Tumor Protein 53
*DPC4: Deleted in Pancreatic Cancer Locus 4

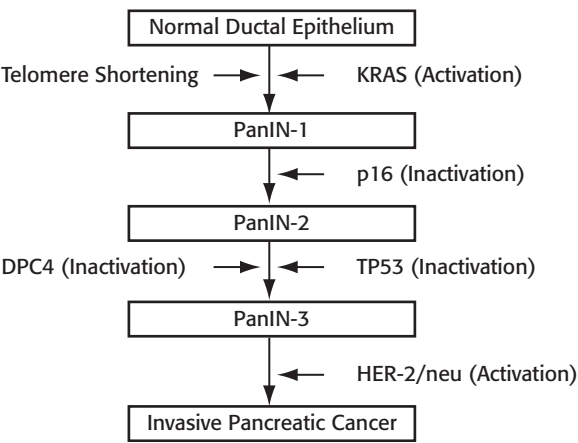


Figure 1.1. Step-wise cytogenetic progression of normal ductal epithelium through PanINs to invasive pancreatic cancer [Refs. 2, 25]

4 Pancreatic Cancer

weight loss, jaundice, chronic exocrine insufficiency and diabetes mellitus [4]. Patients with IPMN are at an increased risk of developing extra-pancreatic cancers, particularly colonic, gastric and lung malignancy [15, 16].

Intraductal papillary mucinous neoplasms may involve the main pancreatic duct, branch ducts or both. They are histologically classified into benign, borderline and malignant categories [1]. Branch duct tumors commonly show less aggressive pathologic changes compared with the main duct subtype [17]. In a large surgical series, 37% of main duct IPMNs developed invasive tumors, whereas only 15% of branch duct IPMNs harbored carcinoma in-situ changes [17]. A recent taxonomic schema of IPMNs identifies four different types of lining epithelium – gastric, pancreaticobiliary, intestinal and oncocytic [18]. It is postulated that different types of IPMN show distinct histogenetic pathways of progression. Most benign, branch-duct IPMNs show gastric type of epithelium, whereas IPMNs with intestinal and pancreaticobiliary epithelium show progression to ‘colloid’ carcinomas and PCs respectively [2, 19].

As with PCs, activating mutations in the KRAS oncogene constitutes an early event in pathogenesis of IPMNs [20]. However, there are some important differences between the cytogenetics of IPMNs and PCs. Loss of DPC4 protein is a characteristic finding associated with 55% of invasive PCs, whereas IPMNs are characterized by universal expression of DPC4 protein [21]. Also, inactivation of the Peutz–Jeghers gene STK11/LKB1 (a phenomenon that is rarely seen with PC) has recently been reported in about 30% of IPMNs [22, 23].

Mucinous cystic neoplasms

Mucinous cystic neoplasms (MCNs) occur almost exclusively in perimenopausal women in the 5th or 6th decades with a 9:1 female preponderance [1]. Mucinous cystic neoplasms comprise 10–45% of cystic pancreatic neoplasms. Most tumors are symptomatic on presentation and occur preferentially (> 90% of cases) in the body and tail of the pancreas [2, 5].

Mucinous cystic neoplasm histologically consists of tall mucin-producing epithelia that are supported by a characteristic ovarian-type stroma that expresses estrogen and progesterone receptors [1]. Microscopically, MCN can be categorized into three types: benign (cystadenoma), borderline (MCN with moderate dysplasia) and malignant (mucinous cystadenocarcinomas) [1].

Mucinous cystic neoplasms demonstrate a histogenetic progression model, akin to PanINs. Mutation of the KRAS oncogene is an early event being seen with 20%, 33% and 89% of adenomatous MCNs, borderline MCNs and MCNs with

Table 1.2. Summary of genetic alterations in sporadic pancreatic cancer [3, 25]

Gene	Mechanism of alteration	% of PC
Oncogenes		
KRAS	Point mutation	> 90
*HER-2/neu	Overexpression	70 (invasive PC)
Tumor suppressor genes		
p16	Homozygous deletion	40
	Loss of heterozygosity	40
	Promoter hypermethylation	15
TP53	Loss of heterozygosity, mutation	50–80
DPC4	Homozygous deletion	35
	Loss of heterozygosity	20

*HER-2/neu: HER: Homolog of human epidermal growth factor receptor;
neu: derived from murine neuroglioblastoma cell line.

carcinoma-in-situ respectively. Inactivation of p53 and DPC4 is seen in invasive MCNs only [24].

In summary, MCNs and IPMNs (with intestinal and pancreaticobiliary epithelium) are considered precursor lesions of PC (and its variants). The genetic changes that underlie the transformation of MCN and IPMN to PC are to some extent similar to the genetic changes responsible for PanIN to PC transformation.

Cytogenetics of pancreatic cancer

Recent advances in cytogenetics and molecular biology have provided unique insights into the pathogenesis of PC. Pancreatic cancer is now thought to be a byproduct of genetic events that may be classified as promotion of proto-oncogenes (KRAS), suppression of tumor suppressor genes (p16, p53, DPC4, DUSP6), or alterations in growth factors (FGF, TGF-β and EGFR) [25]. Table 1.2 lists the known cytogenetics in sporadic PC.

Hereditary pancreatic cancer syndromes

Up to 10% of PCs may show familial clustering [26]. Pancreatic cancer may be associated with several systemic hereditary cancer syndromes such as Peutz–Jeghers syndrome, hereditary breast–ovarian cancer syndrome, ataxia-telangiectasia,

6 Pancreatic Cancer

familial atypical multiple mole melanoma syndrome, familial adenomatous polyposis syndrome and Lynch syndrome [1]. Hereditary pancreatitis and cystic fibrosis are also associated with increased predisposition to PC [7]. Familial PC syndrome is a genetically and phenotypically heterogeneous, autosomal dominant, hereditary disorder characterized by an increased risk of PC. BRCA2 germline mutations have been the most common, isolated genetic abnormality in these patients [27]. Molecular and genetic abnormalities involved in many hereditary syndromes have been characterized [1]. Different syndromes show characteristic genetic abnormality with variable penetrance and phenotypic risk of PC. Table 1.3 summarizes the cytogenetics and the risk of PC in genetic syndromes with predisposition to PC.

Patients with hereditary predisposition to PC tend to develop multicentric cancers at an early age (40–50 years) [26]. They also are at increased risk of developing cutaneous and other systemic cancers. Although screening techniques have been suboptimal and have not been standardized, several approaches to early diagnosis and prophylactic treatment currently are being employed [26]. It is hoped that a thorough knowledge of hereditary PC syndromes may lead to routine screening of high-risk individuals, improved early diagnosis and better cancer control measures.

Implications of cytogenetics on diagnosis and management

Pancreatic cancer is one of the most difficult cancers to treat due to late diagnosis, aggressive tumor biology and poor response to existing systemic therapy. Better understanding of the molecular mechanisms of the development and progression of PCs has allowed for the emergence of novel diagnostic and therapeutic paradigms. Genetic analysis of pancreatic fluid is a promising aid for accurate and early diagnosis of PC. Mesothelin, a protein that is over-expressed in 55% of PCs potentially can be used as a diagnostic marker of PC [2]. In addition, immunoliposomes may be used to selectively target mesothelin-bearing cancer cells [28]. Point mutations of the KRAS gene (found in over 90% of PCs) can be detected on analysis of pancreatic fluid [29]. Tissue-based proteomics may be used to define the “signature” of the PC proteome so that treatment may be tailored [30]. Specific, molecularly targeted drugs and novel gene therapy techniques are being developed to improve patient survival.

Conclusions

Pancreatic cancer arises from precursor lesions (PanIN, MCN, IPMN), is associated with KRAS mutations (early changes), p53 mutations (late changes), and

Table 1.3. Genetic syndromes with inherited predisposition to pancreatic cancer [1, 26]

Hereditary pancreatic cancer syndromes	Implicated gene	Gene location	Systemic syndrome	Lifetime risk of ductal adenocarcinoma
Familial PC syndrome	BRCA-2?	13q12		> 50%
Hereditary pancreatitis	Cationic trypsinogen	7q35	Chronic pancreatitis	30%
Early-onset familial PC / Diabetes syndrome (Seattle family)	Unknown	NA	Chronic pancreatitis	30%; high risk of pancreatitis and diabetes mellitus
Peutz–Jeghers syndrome	STK11/LK B1	19p	GI tract hamartomatous polyps and perioral pigmentation	36%
Hereditary breast–ovarian cancer syndrome	BRCA-2	13q12	Hereditary breast and ovarian cancers	5–10%
Hereditary non-polyposis colorectal cancer (HNPCC) syndrome	MSH2, MLH1	11q22–23	Colorectal cancers and other extracolonic cancers	< 5%
Familial adenomatous polyposis syndrome	APC	5q21	Adenomatous polyps of the GI tract, colorectal cancers	< 5%
Familial atypical multiple mole melanoma (FAMMM) syndrome	p16	9p	Melanomas	10%
Ataxia-telangiectasia	ATM, ATB	11q22	Ataxia-telangiectasia	< 5%

shows an aggressive biological behavior with resultant poor prognosis. Cytogenetic abnormalities that are associated with step-wise, morphological progression of PC from precursor lesions have been elucidated. Several hereditary pancreatic syndromes and their underlying genetic and molecular abnormalities have been

8 Pancreatic Cancer

characterized. It is hoped that knowledge obtained from ongoing and future research into genetic and molecular mechanisms of PC will provide new perspectives that may lead to early diagnosis and better patient outcomes.

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2

Pathology of pancreatic neoplasms

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The term “pancreatic cancer” usually refers to ductal adenocarcinoma. While this entity accounts for 85% of primary pancreatic tumors, a variety of other neoplasms can arise from the range of cell types present in the normal pancreas (ducts, acini and islets) (Table 2.1) [1].

Ductal adenocarcinoma

Approximately two-thirds of ductal adenocarcinomas are found in the head of the pancreas. The tumor tends to be very firm and ill-defined (Figure 2.1) Cystic change (usually due to tumor necrosis) can occur but is rare [2]. This is an aggressively infiltrating cancer with a propensity for direct invasion into distal common bile duct, ampulla of Vater, duodenum, blood vessels, nerves and extrapancreatic soft tissue, particularly posterior to the pancreas.

Ductal adenocarcinoma is a gland-forming tumor. The glands tend to be round or only slightly angulated, giving the tumor a deceptively indolent appearance (Figure 2.2). There is almost always a dense stromal response to the tumor; this “desmoplastic stroma” of myofibroblasts and collagen can make it difficult to pick out the malignant cells. The glands may be lined by a single layer of cuboidal to columnar epithelium or may show complex papillary growth. Tumor nuclei usually vary in size and shape; in fact, the single most helpful diagnostic finding in a biopsy or cytologic preparation is a 4:1 variation in nuclear size within a single gland (Figure 2.3). Other helpful findings include an infiltrative, haphazard arrangement of the glands (as opposed to the lobular arrangement of normal pancreas), glands growing next to muscular arteries (a feature not part of normal pancreatic architecture) and the presence of foamy cytoplasm in the neoplastic cells [3].

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