Table 19-4 Inherited Predisposition to Pancreatic Cancer

Disorder	Gene	Increased Risk of Pancreatic Cancer (Fold)	Risk of Pancreatic Cancer by Age 70 (%)
Peutz-Jeghers syndrome	*STK11*	130	30-60
Hereditary pancreatitis	*PRSS1*, *SPINK1*	50-80	25-40
Familial atypical multiple-mole melanoma syndrome	*CDKN2A*	20-35	10-17
Strong family history (3 or more relatives with pancreatic cancer)	Unknown	14-32	8-16
Hereditary breast and ovarian cancer	Multiple, including *BRCA1*, *BRCA2*, *PALP2*, *BRCA2*	4-10	5
Hereditary non-polyposis colorectal cancer (HNPCC)	Multiple, including *MLH1*, *MSH2* (2p21)	8-10	4

pancreas are usually hard, stellate, gray-white, poorly defined masses (Fig. 19-13*A*).

The vast majority of carcinomas are ductal adenocarcinomas that recapitulate to some degree normal ductal epithelium by forming glands and secreting mucin. Two features are characteristic of pancreatic cancer; it is highly invasive (even "early" invasive pancreatic cancers extensively invade peripancreatic tissues), and it elicits an intense host reaction in the form of dense fibrosis ("desmoplastic response"), described later.

Most carcinomas of the head of the pancreas obstruct the distal common bile duct as it courses through the head of the pancreas. As a consequence there is marked distention of the biliary tree in about 50% of patients with carcinoma of the head of the pancreas, and most develop jaundice. In marked contrast, **carcinomas of the body and tail of the pancreas do not impinge on the biliary tract and hence remain silent for some time. They may be quite large and most are widely disseminated by the time they are discovered.** Pancreatic cancers often grow along nerves and invade into blood vessels and the retroperitoneum. They can directly invade the spleen, adrenals, transverse colon, and stomach. Peripancreatic, gastric, mesenteric, omental, and portohepatic lymph nodes are frequently involved. Distant metastases occur, principally to the liver and lungs.

Microscopically, there is no difference between carcinomas of the head of the pancreas and those of the body and tail of the pancreas. The appearance is usually that of a **moderately to poorly differentiated adenocarcinoma forming abortive tubular structures or cell clusters and showing an aggressive, deeply infiltrative growth pattern** (Fig. 19-13*B*). The malignant glands are poorly formed and are usually lined by pleomorphic cuboidal-to-columnar epithelial cells. Well-differentiated carcinomas are the exception. As noted earlier, a characteristic feature of these cancers is that they elicit an intense desmoplastic reaction with dense stromal fibrosis. The marked degree of desmoplasia can hinder the interpretation of diagnostic biopsies, as much of the tissue present is nonneoplastic. Perineural invasion within and beyond the organ is common, as are lymphatic and large vessel invasion.

Less common morphologic variants of pancreatic cancer include adenosquamous carcinomas, colloid carcinoma, hepatoid carcinoma, medullary carcinoma, signet-ring cell carcinoma, undifferentiated carcinoma, and undifferentiated carcinoma with osteoclast-like giant cells.

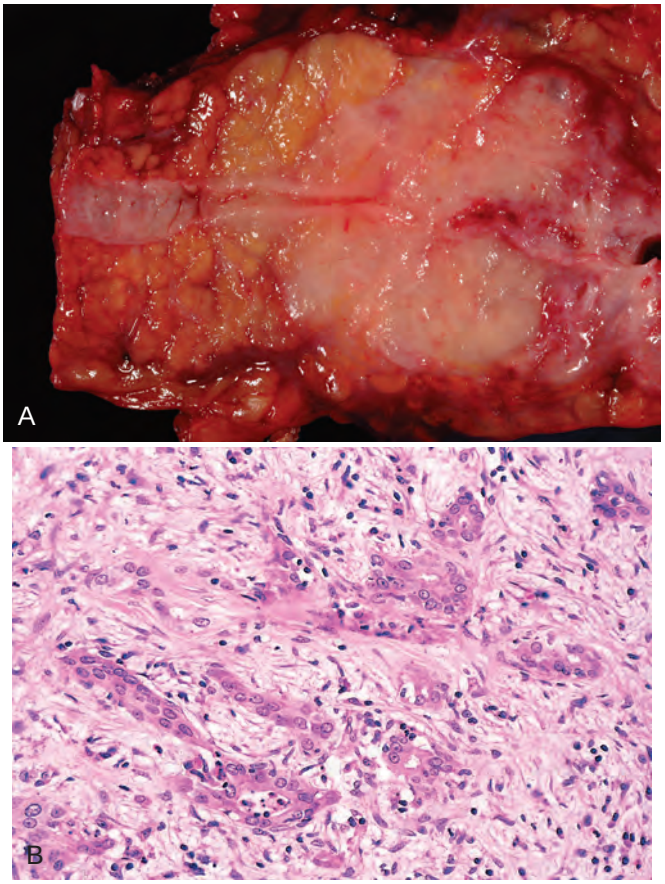

Figure 19-13 Carcinoma of the pancreas. **A,** A cross-section through the tail of the pancreas showing normal pancreatic parenchyma and a normal pancreatic duct *(left)*, an ill-defined mass in the pancreatic substance *(center)* with narrowing of the pancreatic duct, and dilatation of the pancreatic duct upstream *(right)* from the mass. **B,** Poorly formed glands are present in densely fibrotic stroma within the pancreatic substance; some inflammatory cells are also present.

Clinical Features. From the preceding discussion it should be evident that **carcinomas of the pancreas remain silent until they invade into adjacent structures**. *Pain* is usually the first symptom, but by the time pain appears these cancers are usually beyond cure. *Obstructive jaundice* is associated with most cases of carcinoma of the head of the pancreas, but it rarely draws attention to the invasive cancer soon enough. Weight loss, anorexia, and generalized malaise and weakness tend to be signs of advanced disease. *Migratory thrombophlebitis,* known as the *Trousseau sign,* occurs in about 10% of patients and is attributable to the elaboration of platelet-activating factors and procoagulants from the