KEY CONCEPTS

- Virtually all serous cystic neoplasms are benign.
- Intraductal papillary mucinous neoplasms and mucinous cystic neoplasms are curable noninvasive cystic neoplasms that can progress to incurable invasive carcinoma.
- Each of the major cystic neoplasms has a relatively specific mutational profile.

Pancreatic Carcinoma

Infiltrating ductal adenocarcinoma of the pancreas, more commonly known as pancreatic cancer, is the fourth leading cause of cancer deaths in the United States, trailing only lung, colon, and breast cancers, and has one of the highest mortality rates of any cancer. It was estimated that in 2013 pancreatic cancer would strike approximately 44,000 Americans, virtually all of whom would die of their disease. The 5-year survival rate is dismal, less than 5%.

Precursors to Pancreatic Cancer

Invasive pancreatic cancers are believed to arise from well-defined noninvasive precursor lesions in small ducts referred to as *pancreatic intraepithelial neoplasia* (PanIN, Fig. 19-11). Just as there is a progression in the colorectum from nonneoplastic epithelium to adenoma to invasive carcinoma (Chapters 7 and 17), there is a progression in the pancreas from nonneoplastic epithelium to PanIN to invasive carcinoma. The PanIN-invasive carcinoma sequence is supported by the following observations:

- The genetic and epigenetic alterations identified in PanIN are similar to those found in invasive cancers (described later).
- PanIN is often found in pancreatic parenchyma adjacent to infiltrating carcinoma.
- PanIN precedes the development of invasive cancer in genetically engineered mouse models of pancreatic cancer.
- Isolated case reports have documented individuals with PanIN who later developed an invasive pancreatic cancer.

The epithelial cells in PanIN show dramatic telomere shortening. A critical shortening of telomere length in PanIN may predispose these lesions to accumulate progressive chromosomal abnormalities and to develop invasive carcinoma (Chapter 7).

Based on these observations, a model for progression of PanINs has been proposed (Fig. 19-12).

Pathogenesis

Multiple genes are somatically mutated or epigenetically silenced in each pancreatic carcinoma, consistent with their stepwise evolution from precursor lesions, and the patterns of genetic alterations in pancreatic carcinoma as a group differs from those seen in other malignancies. Molecular alterations in pancreatic carcinogenesis are summarized in Table 19-3 and include the following:

KRAS. *KRAS* (chromosome 12p) is the most frequently altered oncogene in pancreatic cancer, with activating point mutations being present in 90% to 95% of cases. These point mutations result in constitutive activation of

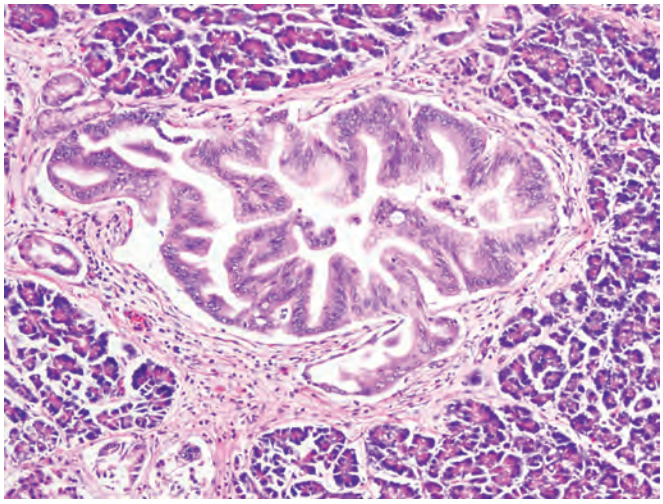

Figure 19-11 Pancreatic intraepithelial neoplasia grade 3 (PanIN-3) involving a small pancreatic duct.

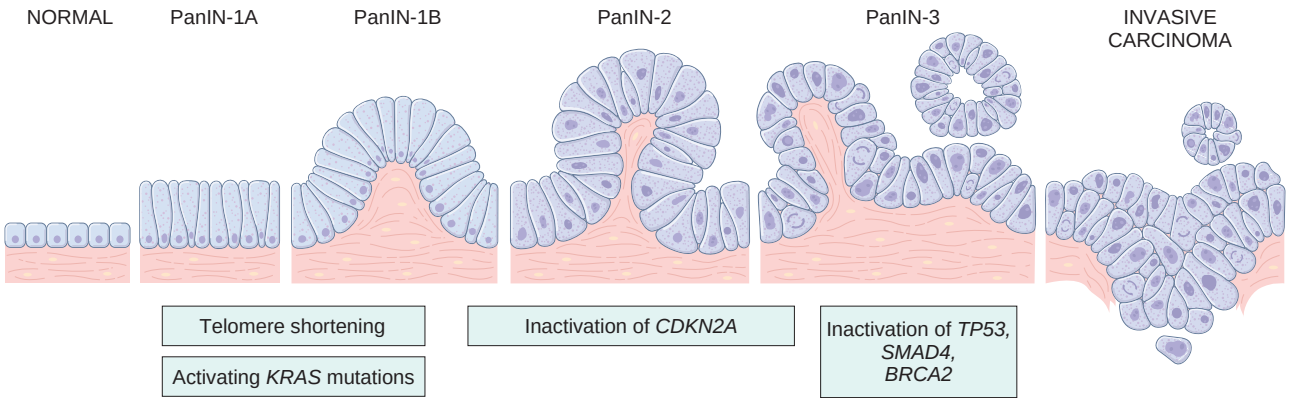

Figure 19-12 Model for the progression from normal ducts *(far left)* through PanINs *(center)* to invasive carcinoma *(far right).* It is postulated that telomere shortening and mutations of the oncogene *KRAS* occur early, that inactivation of the *CDKN2A* tumor suppressor gene that encodes the cell cycle regulator p16 sta occurs in intermediate grade lesions, and that the inactivation of the *TP53*, *SMAD4*, and *BRCA2* tumor suppressor genes occur in higher grade (PanIN-3) lesions. It is important to note that while there is a general temporal sequence of changes, the accumulation of multiple mutations is more important than their occurrence in a specific order. (Adapted from Wilentz RE, et al: Loss of expression of DPC4 in pancreatic intraepithelial neoplasia: evidence that *DPC4* inactivation occurs late in neoplastic progression. Cancer Res 2000;60:2002.)