

Figure 17-9 Esophageal cancer. **A**, Adenocarcinoma usually occurs distally and, as in this case, often involves the gastric cardia. **B**, Squamous cell carcinoma is most frequently found in the mid-esophagus, where it commonly causes strictures.

Squamous Cell Carcinoma

In the United States, esophageal squamous cell carcinoma occurs in adults older than age 45 and affects males four times more frequently than females. Risk factors include alcohol and tobacco use, poverty, caustic esophageal injury, achalasia, tylosis, Plummer-Vinson syndrome, diets that are deficient in fruits or vegetables, and frequent consumption of very hot beverages. Previous radiation to the mediastinum also predisposes individuals to esophageal carcinoma, with most cases occurring 5 to 10 or more years after exposure. Esophageal squamous cell carcinoma is nearly eight-fold more common in African Americans than Caucasians, a striking risk disparity that reflects differences in rates of alcohol and tobacco use as well as other poorly understood factors.

Esophageal squamous cell carcinoma incidence varies up to 180-fold between and within countries, being more common in rural and underdeveloped areas. The regions with highest incidence are Iran, central China, Hong Kong, Brazil, and South Africa. A pocket of extremely high esophageal squamous cell carcinoma incidence in western Kenya includes patients younger than 30 years of age and has been linked to consumption of a traditional fermented milk, termed mursik, which contains the carcinogen acetaldehyde (Chapter 9).

Pathogenesis. The majority of esophageal squamous cell carcinomas in Europe and the United States are linked to the use of alcohol and tobacco, which synergize to increase the risk. However, esophageal squamous cell carcinoma is also common in some regions where alcohol and tobacco use is uncommon. Thus, nutritional deficiencies, as well as polycyclic hydrocarbons, nitrosamines, and other

mutagenic compounds, such as those found in fungus-contaminated foods, must also be considered. Human papillomavirus (HPV) infection has also been implicated in esophageal squamous cell carcinoma in high-risk areas but not in low-risk regions. The molecular pathogenesis of esophageal squamous cell carcinoma remains incompletely defined, but recurrent abnormalities include amplification of the transcription factor gene *SOX2* (believed to be involved in cancer stem cell self-renewal and survival); overexpression of the cell cycle regulator cyclin D1; and loss-of-function mutations in the tumor suppressors *TP53*, *E-cadherin*, and *NOTCH1*.

MORPHOLOGY

In contrast to adenocarcinoma, half of squamous cell carcinomas occur in the middle third of the esophagus (Fig. 17-9B). Squamous cell carcinoma begins as an in situ lesion termed **squamous dysplasia** (this lesion is referred to as intraepithelial neoplasia or carcinoma in situ at other sites). Early lesions appear as small, gray-white, plaque-like thickenings. Over months to years they grow into tumor masses that may be

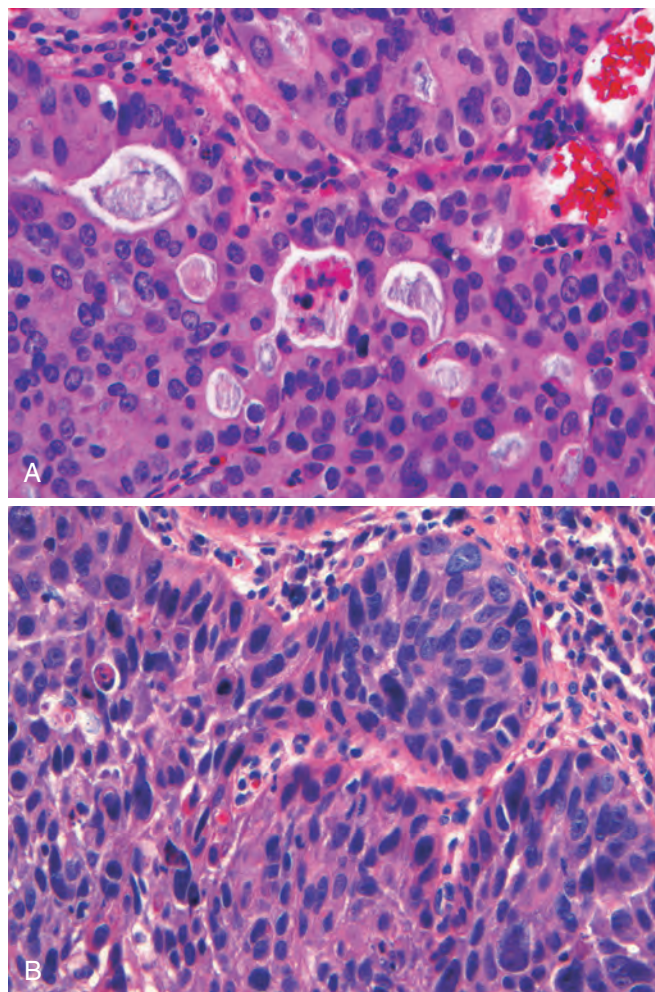


Figure 17-10 Esophageal cancer. **A**, Esophageal adenocarcinoma organized into back-to-back glands. **B**, Squamous cell carcinoma composed of nests of malignant cells that partially recapitulate the organization of squamous epithelium.