crowding. High-grade dysplasia is characterized by more severe cytologic atypia and irregular architecture, including glandular budding and gland-within-gland, or cribriform, structures. Like intestinal adenomas, gastric adenomas are premalignant neoplastic lesions. However, the risk of transformation to invasive cancer is much higher in gastric adenomas.

Gastric Adenocarcinoma

Adenocarcinoma is the most common malignancy of the stomach, comprising more than 90% of all gastric cancers. As discussed in more detail later, gastric adenocarcinoma is often separated morphologically into intestinal type, which tends to form bulky masses, and a diffuse type, which infiltrates the wall diffusely, thickens it, and is typically composed of signet ring cells. Early symptoms of both types of gastric adenocarcinoma resemble those of chronic gastritis and peptic ulcer disease, including dyspepsia, dysphagia, and nausea. As a result, these tumors are often discovered at advanced stages, when symptoms such as weight loss, anorexia, early satiety (primarily in diffuse cancers), anemia, and hemorrhage trigger further diagnostic evaluation.

Epidemiology. Gastric cancer incidence varies markedly with geography. In Japan, Chile, Costa Rica, and Eastern Europe, the incidence is up to 20-fold higher than in North America, northern Europe, Africa, and Southeast Asia. Mass endoscopic screening programs have been successful in regions where the incidence is high, such as Japan, where 35% of newly detected cases are early gastric cancers, limited to the mucosa and submucosa. Unfortunately, mass screening programs are not cost-effective in regions where the incidence is low, and fewer than 20% of cases are detected at an early stage in North America and northern Europe. Metastases are often detected at time of diagnosis. Sites most commonly involved include the supraclavicular sentinel lymph node (Virchow node), periumbilical lymph nodes (Sister Mary Joseph nodule), the left axillary lymph node (Irish node), the ovary (Krukenberg tumor), or the pouch of Douglas (Blumer shelf).

Gastric cancer is more common in lower socioeconomic groups and in individuals with multifocal mucosal atrophy and intestinal metaplasia. *Gastric dysplasia and adenomas are recognizable precursor lesions associated with gastric adenocarcinoma.* PUD does not impart an increased risk of gastric cancer, but patients who have had partial gastrectomies for PUD have a slightly higher risk of developing cancer in the residual gastric stump, possibly due to hypochlorhydria, bile reflux, and chronic gastritis.

In the United States, gastric cancer rates dropped by more than 85% during the twentieth century. Adenocarcinoma of the stomach was the most common cause of cancer death in the United States in 1930 and remains a leading cause of cancer death worldwide, but now accounts for fewer than 2.5% of cancer deaths in the United States. Similar declines have been reported in many other Western countries, suggesting that environmental and dietary factors contribute to the development of gastric cancers. Consistent with this conclusion, studies of migrants from high-risk to low-risk regions have shown that gastric cancer rates in second-generation immigrants are similar to those in their new country of residence.

The cause of the overall reduction in gastric cancer is most closely linked to decreases in H. pylori prevalence. Another possible contributor is the decreased consumption of dietary carcinogens, such as N-nitroso compounds and benzo[*a*]pyrene, because of the reduced use of salt and smoking for food preservation and the widespread availability of food refrigeration.

Although overall incidence of gastric adenocarcinoma is falling, cancer of the gastric cardia is on the rise. This is probably related to Barrett esophagus and may reflect the increasing incidence of chronic GERD and obesity. Consistent with this presumed common pathogenesis, distal esophageal adenocarcinomas and gastric cardia adenocarcinomas are similar in morphology, clinical behavior, and therapeutic response.

Pathogenesis. While the majority of gastric cancers are not hereditary, the mutations identified in familial gastric cancer have provided important insights into mechanisms of carcinogenesis in sporadic cases. Familial gastric cancer is strongly associated with germline loss-of-function mutations in the tumor suppressor gene *CDH1*, which encodes the cell adhesion protein E-cadherin (discussed in Chapter 7). Loss-of-function mutations in *CDH1* are also present in about 50% of sporadic diffuse gastric tumors, while E-cadherin expression is drastically decreased in the rest, often by hyper methylation and silencing of the *CDH1* promoter. *Thus, the loss of E-cadherin is a key step in the development of diffuse gastric cancer. CDH1* mutations are also common in sporadic and familial lobular carcinoma of the breast, which, like diffuse gastric cancer (see later), tends to infiltrate as single cells, and individuals with *BRCA2* mutations are at increased risk of developing diffuse gastric cancer. Mutation of *TP53* is also found in the majority of sporadic gastric cancers of both diffuse and intestinal types.

In contrast to diffuse gastric cancers, sporadic intestinal-type gastric cancers are strongly associated with mutations that result in increased signaling via the Wnt pathway. These include loss-of-function mutations in the adenomatous polyposis coli (APC) tumor suppressor gene and gain-of-function mutations in the gene encoding β-catenin. Loss-of-function mutations or silencing of a number of other tumor suppressor genes have also been identified, including those involved in TGFβ signaling (TGFβRII), regulation of apoptosis (BAX), and cell cycle control (CDKN2A), all of which are discussed in more detail in Chapter 7. As expected, FAP patients, who carry germline *APC* mutations, have an increased risk of intestinal-type gastric cancer. This is particularly true in Japan and other high-risk areas, as compared to individuals with FAP residing in areas of low gastric cancer incidence. Thus, both host genetic background and environmental factors affect risk. As discussed in the context of *H. pylori* gastritis, genetic variants of proinflammatory and immune response genes, including those that encode IL-1β, TNF, IL-10, IL-8, and Toll-like receptor 4 (TLR4), are associated with elevated risk of gastric cancer when accompanied by *H. pylori* infection. Thus, it is clear that chronic inflammation promotes gastric neoplasia. Other associations between chronic inflammation and cancer are discussed in Chapter 7.