that encodes a bacterial type IV secretion system. Through this system, an effector protein, CagA, is translocated into epithelial cells, where it may be transformed by phosphorylation and induces host cell signal transduction; proliferative, cytoskeletal, and inflammatory changes in the cell result. The protein at the tip of the secretory apparatus, CagL, binds to integrins on the cell surface, transducing further signaling. Finally, soluble components of the peptidoglycan cell wall enter the cell, mediated by the same secretory system. These components are recognized by the emergency intracellular bacterial receptor Nod1, which stimulates a proinflammatory cytokine response resulting in enhanced gastric inflammation. Carriage of *cag*-positive strains increases the risk of peptic ulcer or gastric adenocarcinoma. A second major virulence factor is the vacuolating cytotoxin VacA, which forms pores in cell membranes. VacA is polymorphic, and carriage of more active forms also increases the risk of disease. Other bacterial factors that are associated with increased disease risk include adhesins, such as BabA (which binds to blood group antigens on epithelial cells), and incompletely characterized factors, such as another recently described bacterial type 4 secretion system.

Host Genetic and Environmental Factors The best-characterized host determinants of disease are genetic polymorphisms leading to enhanced activation of the innate immune response, including polymorphisms in cytokine genes or in genes encoding bacterial recognition proteins such as Toll-like receptors. For example, colonized people with polymorphisms in the interleukin 1 gene that increase the production of this cytokine in response to *H. pylori* infection are at increased risk of gastric adenocarcinoma. In addition, environmental cofactors are important in pathogenesis. Smoking increases the risks of duodenal ulcers and gastric cancer in *H. pylori*–positive individuals. Diets high in salt and preserved foods increase cancer risk, whereas diets high in antioxidants and vitamin C are modestly protective.

Distribution of Gastritis and Differential Disease Risk The pattern of gastric inflammation is associated with disease risk: antral-predominant gastritis is most closely linked with duodenal ulceration, whereas pan-gastritis is linked with gastric ulceration and adenocarcinoma. This difference probably explains why patients with duodenal ulceration are not at high risk of developing gastric adenocarcinoma later in life, despite being colonized by *H. pylori*.

PATHOGENESIS OF DUODENAL ULCERATION How gastric colonization causes duodenal ulceration is now becoming more clear. *H. pylori*–induced inflammation of the gastric antrum diminishes the number of somatostatin-producing D cells. Because somatostatin inhibits gastrin release, gastrin levels are higher than in *H. pylori*–negative persons, and these higher levels lead to increased meal-stimulated acid secretion from the relatively spared gastric corpus. How this situation increases duodenal ulcer risk remains controversial, but the increased acid secretion may contribute to the formation of the potentially protective gastric metaplasia found in the duodenum of duodenal ulcer patients. Gastric metaplasia in the duodenum may become colonized by *H. pylori* and subsequently inflamed and ulcerated.

PATHOGENESIS OF GASTRIC ULCERATION AND GASTRIC ADENOCARCINOMA The pathogenesis of these conditions is less well understood, although both arise in association with pan- or corpus-predominant gastritis. The hormonal changes described above still occur, but the inflammation in the gastric corpus means that it produces less acid (hypochlorhydria) despite hypergastrinemia. Gastric ulcers usually occur at the junction of antral and corpus-type mucosa, an area that is often particularly inflamed. Gastric cancer probably stems from progressive DNA damage and the survival of abnormal epithelial cell clones. The DNA damage is thought to be due principally to reactive oxygen and nitrogen species arising from inflammatory cells, perhaps in relation to other bacteria that survive in a hypochlorhydric stomach. Longitudinal analyses of gastric biopsy specimens taken years apart from the same patient show that the common *intestinal* type of gastric adenocarcinoma follows stepwise changes from simple gastritis to gastric atrophy, intestinal metaplasia, and dysplasia. A second, *diffuse* type of gastric adenocarcinoma found more commonly in younger adults may arise directly from chronic gastritis without atrophic changes.

CLINICAL MANIFESTATIONS

Essentially all *H. pylori*–colonized persons have histologic gastritis, but only ~10–15% develop associated illnesses such as peptic ulceration, gastric adenocarcinoma, or gastric lymphoma (Fig. 188-1). Rates among women are less than half of those among men for both diseases.

Peptic Ulcer Disease Worldwide, >80% of duodenal ulcers and >60% of gastric ulcers are related to *H. pylori* colonization (Chap. 348). However, in particular, the proportion of gastric ulcers caused by aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is increasing, and in many developed countries these drugs have overtaken *H. pylori* as a cause of gastric ulceration. The main lines of evidence supporting an ulcer-promoting role for *H. pylori* are that (1) the presence of the organism is a risk factor for the development of ulcers, (2) non-NSAID-induced ulcers rarely develop in the absence of *H. pylori*, (3) eradication of *H. pylori* virtually abolishes long-term ulcer relapse, and (4) experimental *H. pylori* infection of gerbils can cause gastric ulceration.

Gastric Adenocarcinoma and Lymphoma Prospective nested case-control studies have shown that *H. pylori* colonization is a risk factor for adenocarcinomas of the distal (noncardia) stomach (Chap. 109). Long-term experimental infection of gerbils also may result in gastric adenocarcinoma. Moreover, *H. pylori* may induce primary gastric

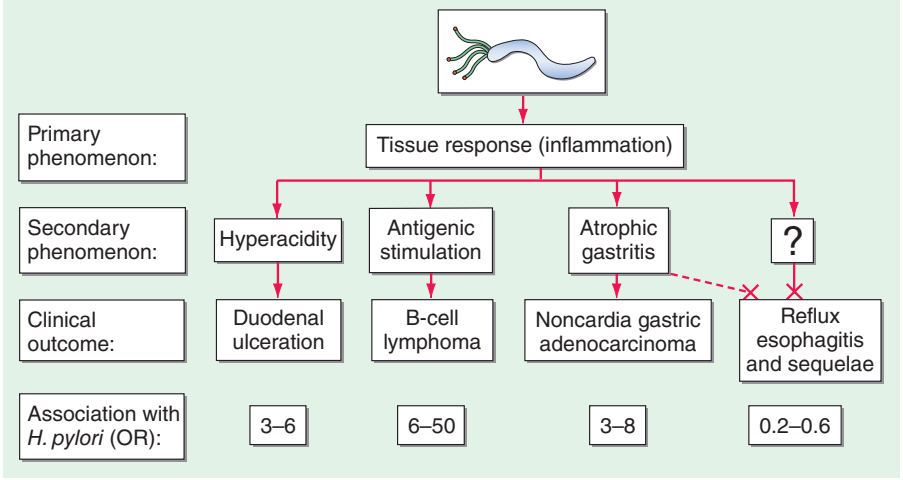

FIGURE 188-1 Schematic of the relationships between colonization with *Helicobacter pylori* and diseases of the upper gastrointestinal tract. Essentially all persons colonized with *H. pylori* develop a host response, which is generally termed *chronic gastritis*. The nature of the host's interaction with the particular bacterial population determines the clinical outcome. *H. pylori* colonization increases the lifetime risk of peptic ulcer disease, noncardia gastric cancer, and B-cell non-Hodgkin's gastric lymphoma (odds ratios [ORs] for all, >3). In contrast, a growing body of evidence indicates that *H. pylori* colonization (especially with *cagA*$^+$ strains) protects against adenocarcinoma of the esophagus (and the sometimes related gastric cardia) and premalignant lesions such as Barrett's esophagus (OR, <1). Although the incidences of peptic ulcer disease (cases not due to nonsteroidal anti-inflammatory drugs) and noncardia gastric cancer are declining in developed countries, the incidence of adenocarcinoma of the esophagus is increasing. *(Adapted from MJ Blaser: Hypothesis: The changing relationships of Helicobacter pylori and humans: Implications for health and disease. J Infect Dis 179:1523, 1999, with permission.)*