It is becoming increasingly evident that *Helicobacter pylori* have been normal inhabitants of the human stomach since the earliest times (1) and that, over the course of the twentieth century, *H. pylori* has been disappearing (2). Because large groups of people can be identified who either do or do not carry the organism, we now can assess the consequences of its presence (and absence). Such studies have shown that the presence of *H. pylori* is associated with the development of all of the important precursor lesions for adenocarcinoma of the stomach, including chronic gastritis, atrophic gastritis, and intestinal metaplasia and that, in consequence, it is the major risk factor for non-cardia gastric cancers (3,4).

However, most *H. pylori*-positive individuals never develop gastric cancer (or peptic ulcer disease, for which it also is a risk factor). Why does illness develop in only some colonized individuals? Possible explanations include the characteristics of the colonizing *H. pylori* strains, the genotype of the host, exposure to environmental cofactors (e.g. those present in tobacco smoke or diet), or interactions among two or more of these factors. Discerning among these possibilities is important, because there also is increasing evidence that the absence of *H. pylori* may be associated with increased risks of diarrheal disease in children (5) and of reflux esophagitis and its sequelae—Barrett’s esophagus and adenocarcinoma of the esophagus—in adults (6-10). Because of these potential benefits, campaigns to rid humans of *H. pylori* also is increasing evidence that the absence of *H. pylori* may be associated with increased risks of diarrheal disease in children (5) and of reflux esophagitis and its sequelae—Barrett’s esophagus and adenocarcinoma of the esophagus—in adults (6-10). Because of these potential benefits, campaigns to rid humans of *H. pylori* may result in a rise in some illnesses as others are reduced. Nevertheless, because persistence of *H. pylori* is clearly involved in the pathogenesis of gastric cancer, medical scientists must be able to establish who is at greatest risk for the adverse consequences of this essentially lifelong colonization.

In this issue of the Journal, Figueiredo and colleagues explored this problem (11). Beginning with a population that was *H. pylori*-positive, they sought to find modifying factors whose presence was associated with the diagnosis of gastric cancer. They examined bacterial genotypes that could be readily measured and for which prior work, including their own, suggested risk modification for gastric cancer (12-16). Similarly, they studied host genotypes previously shown to affect gastric cancer risk (17,18) and, importantly, also examined the interactions between microbial and host genotypes. In so doing, they both confirmed the prior work and extended our knowledge of gastric cancer risk factors, identifying combinations with lowest or highest risk, with 20- to 80-fold differences! The effect of combining several factors was synergistic, indicating the promise of such approaches. Why was this study so powerful?

One reason may be that the markers that Figueiredo and colleagues assessed all relate to the intensity of gastric inflammation in *H. pylori*-positive individuals. The host factors studied relate to the functional activity of interleukin 1 (IL-1): IL-1β is a strongly pro-inflammatory cytokine and the IL-1 receptor antagonist binds competitively to IL-1 receptors (19). The genetic loci coding for these proteins and governing their expression are polymorphic, with phenotypic differences that are measurable. The *H. pylori* factors studied relate to the presence of the cag “pathogenicity” island and to the vacA genotype. Strains with the cag island inject the CagA protein into the gastric epithelium (20) and induce higher levels of pro-inflammatory cytokines (including IL-1β) (4), gastric inflammation (21), atrophic gastritis, and intestinal metaplasia (22). There are two major polymorphic sites within vacA, which encodes a vacuolating cytotoxin. These sites affect either the signal sequence (s region) or the middle of the protein (m region) (10). The vacA polymorphic sites are closely linked, and studies of these two markers may thus be examining the same phenomenon. The vacA m genotype, which is less closely linked to cag status, is also a marker of both inflammation and cancer risk (14,15).

The findings of Figueiredo et al. (11) suggest that the interactions between these specific host and bacterial characteristics are biologically significant. Although the study is limited by its retrospective nature and by the multiple *H. pylori* strains colonizing some hosts, the findings are consistent with previous work and are biologically plausible. The data fit best with a negative-feedback (homeostatic) model, in which cross-signaling between the *H. pylori* (bacterial) populations and cells of the colonized host lead to a dynamic equilibrium (23). In this model, the specific bacterial and host genotypes influence the “gain” or amplitude of the interaction, with its secondary pathologic and tertiary clinical consequences. Although human genotypes do not vary over the course of a life, the *H. pylori* subpopulations within a host are complex and changing (24,25). Thus, although the work reported (11) must be considered a first approximation, the model may in fact be a general paradigm for tumors induced by microbes (26). For persistent, well-adapted microbes like *H. pylori* [or Epstein-Barr virus, for example (27)], specific combinations of microbial and host genotypes may shape the equilibrium in ways that augment or lessen risk of disease.

Is the work by Figueiredo et al. (11) ready for the clinic? Although promising, it is still too early to generalize from this work. The study needs confirmation, different ethnic groups must be examined, the techniques must be simplified for general use, and our understanding of the risks and benefits of *H. pylori* must grow (28). In particular, the observations relating cagA and vacA genotypes to disease in the West are not clearly present in East Asia, because a preponderance of Asian strains carry the...
alleles most strongly associated with disease (29). However, Figueiredo’s work is a step in the right direction, and recent work has focused on other host polymorphisms in relation to \textit{H. pylori}-associated diseases (30,31).

Gastric adenocarcinoma remains one of the leading causes of cancer death in the world, and new approaches to its prevention are needed. Translational research that stratifies patients according to pathogenetically relevant factors, as done here, may also lead to new types of therapy. Because \textit{H. pylori} are polymorphic, because subpopulations colonizing a host are ever changing in both phenotype and dominance (32), and because humans are genetically diverse and also show age-related accumulation of somatic mutations, the range of potential interactions is vast. Nevertheless, assessing risk for gastric diseases now is becoming a tractable problem and may ultimately prove to be a paradigm for other microbiologically induced diseases.

\textbf{REFERENCES}


\textbf{Notes}

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