**Helicobacter and Gastric Malignancies**

Steven F. Moss* and Peter Malfertheiner†

*Rhode Island Hospital and Brown University, Providence, RI, USA; †Otto-von-Guericke University of Magdeburg, Magdeburg, Germany

**Abstract**

Over the past year *Helicobacter pylori* has been confirmed as the most important risk factor for non-cardia gastric adenocarcinomas and gastric mucosa-associated lymphoid tissue (MALT) lymphomas. Eradication therapy has been proven to be beneficial when given prior to the development of intestinal metaplasia, but is less efficacious when administered later. However, the best data from clinical trials indicate that *H. pylori* eradication alone will have only a moderate effect on gastric cancer incidence worldwide. The mechanisms responsible for *H. pylori*-associated gastric carcinogenesis continue to be dissected. Accumulating evidence suggests that some *H. pylori* may be able to invade through the gastric epithelial barrier, though pro-carcinogenic effects may also be related to the complex and evolving pathways of altering signal transduction pathways within gastric epithelial cells that are stimulated by adherence and translocation of *H. pylori* products through its type IV secretory system. Determinants of the host response to *H. pylori* infection continue to focus on polymorphisms in genes related to the innate and acquired immune responses, including NOD2, COX-2, and TLR-4. *H. pylori* eradication is indicated for low-grade gastric B-cell MALT lymphoma and may even provide “cure” in some apparently *H. pylori*-negative cases. How and why does *H. pylori* promote lymphomagenesis? Some evidence from human and murine models points to specific chromosomal translocations and host genetic polymorphisms as relating to the outcome of infection. Finally, *Helicobacter hepaticus* infection has been linked to both intestinal and breast tumorigenesis in susceptible strains of female mice – a provocative and novel finding warranting further investigation.

**Epidemiology**

The extent to which chronic *Helicobacter pylori* infection is responsible for the global burden of gastric cancer and non-Hodgkin’s lymphoma was reassessed based on new cancers registered in 2002 [1]. In that year almost 20% of cancers were considered to be attributable to infectious diseases, with *H. pylori* being the leading cause (5.5% of all cancers) followed by human papilloma viruses, hepatitis B and C viruses, Epstein–Barr virus, HIV, and human herpesvirus 8. *H. pylori* was estimated to be responsible for about 75% of noncardia gastric cancers and gastric non-Hodgkin’s lymphomas, and 65% of all stomach cancers worldwide.

Reviewing data from the European Prospective Investigation into Cancer and Nutrition trial, a multicenter case control study that started in 1992, Palli et al. [2] reported that anti-CagA antibodies were associated with a threefold increased risk of gastric cancer development. In contrast, no such association was observed for noncardia cases after adjustment for multiple demographic, nutritional, and other confounding factors. The contribution of *H. pylori* to noncardia gastric cancers was also calculated from a nested case-control study of *H. pylori* infection within the Finnish chemopreventive cancer prevention trial conducted from 1985 to 1999 [3]. This report confirmed the results of most other studies from Western populations, i.e. *H. pylori*-infected subjects had a statistically significantly decreased risk of gastric cardia cancer [adjusted odds ratio (OR) 0.3], but an increased risk of noncardia gastric cancer (adjusted OR 8). In contrast, in China *H. pylori* infection was associated with increased risk of both noncardia and cardia cancers [4] – in line with previous reports from East Asia.

It has long been debated why the incidence of gastric cancer is so high in Japan. Diet, genetic susceptibility, and *H. pylori* infection have all been proposed as causes. Differences in interpretation of the gastric histology by Eastern- and Western-trained pathologists may further render the conclusion difficult. In an interesting comparative...
study. Naylor et al. [5] compared the gastric histology of
dyspeptic patients without ulcers, cancer, or endoscopic
esophagitis attending endoscopy centers in Japan and the
UK. After review by highly experienced Japanese and
English ‘blinded’ pathologists, the Japanese stomachs
clearly had much more extensive and severe gastritis, with
greater numbers of inflammatory cells and a greater risk of
progression to atrophy and intestinal metaplasia. About
90% of the gastritis cases from both countries were related
to *H. pylori* infection; CagA-positive strains were more
common in Japan than in the UK. This prospective
observational study supports the assertion that the
increased gastric cancer risk in Japan relates to the severity
and extent of the underlying chronic gastritis.

Childhood living conditions are well established to be
important determinants of *H. pylori* acquisition. Re-
analyzing data from a long-term cohort of Japanese-
American men followed for almost three decades, the risk
of gastric cancer in men infected by Cag-positive *H. pylori*
strains was especially high in those who had many siblings
(OR 2, when comparing > 6 sibs with one to three sibs in
a single family) [6]. Thus, having many brothers and sisters
increases one’s risk of gastric cancer associated with
Cag-positive *H. pylori* infection, conceivably through
erlier acquisition of *H. pylori*, infection by more virulent
strains, or due to subtle changes in later socioeconomic
status or lifestyle.

**H. pylori** Eradication and the Prevention of
Gastric Cancer

Despite the overwhelming evidence that *H. pylori* infection
is a risk factor for noncardia gastric cancer, accumulating
evidence indicates that although *H. pylori* eradication is
relatively simple to achieve, impacting the global burden
of gastric cancer will be a much more difficult challenge.
One of the earlier studies providing some optimism that
*H. pylori* eradication would decrease gastric cancer risk
was the observation in a large cohort study that the
gastric cancer risk after hip replacement (accompanied by
antibiotic use) was lower than expected [7]. However, the
hypothesis that antibiotics given at the time of surgery
provided incidental eradication of *H. pylori* has not been
supported by a much larger recent study from the same
group [8]. Over half a million Swedish inpatients treated
for infectious diseases between 1970 and 2003 had no
evidence of a subsequent decrease in gastric cancer risk at
all, demonstrating that ‘incidental eradication’, if it occurs,
has no long-term benefits on gastric cancer incidence.

Well-conducted large, prospective, controlled interven-
tional studies to examine the effects of *H. pylori* eradication
on gastric cancer have been few and far between. This may
be partly due to recruitment problems related to the
ethical dilemma of having a placebo arm, as *H. pylori* is
designated as a definite carcinogen. You et al. [9] reported
the largest study so far of *H. pylori* eradication in subjects
at risk for gastric cancer. Following baseline endoscopy,
patients in a high cancer incidence area in China who were
*H. pylori*-positive were randomized in a factorial design to
receive either *H. pylori* eradication therapy: amoxicillin
and omeprazole; and/or garlic extracts; and/or a ‘vitamin
supplementation’ of vitamin C, E, and selenium. Those
who were not infected by *H. pylori* entered either the
‘vitamin’ and/or the ‘garlic’ arm with appropriate placebo
*H. pylori* therapy. After > 7 years follow up (including an
impressive 93% retention of the initial recruits) those
subjects who had received *H. pylori* eradication therapy
had a reduced combined prevalence of gastric cancer and
preneoplastic changes (the primary endpoint). The number
of cases of gastric cancer was low, but *H. pylori* eradication
provided some benefit with an overall reduction in
incidence from 2.4% to 1.7%. However this was not statisti-
cally significant despite the investigators having entered
> 3000 subjects in the trial. In subgroup analysis, those
subjects who had already progressed to intestinal metaplasia
at the time of entry into study had the least benefit from
*H. pylori* eradication therapy. No beneficial effects accrued
from either garlic extracts or the combination of vitamin C,
E, and selenium. These sobering results from a large
prospective interventional study contrast with many of the
observational studies that appeared to indicate a much
greater benefit of *H. pylori* eradication. One example is the
study by Takenaka et al. [10], who observed gastric cancer
in six of 1519 (0.4%) subjects who were treated with
*H. pylori* eradication therapy after having an endoscopy
in Japan versus five of 288 (1.7%) subjects who failed
to systematically review the more rigorously designed
observational and randomized studies of *H. pylori* eradi-
cation. Though one could debate the methodology used
to select published studies for their pooled analyses, the
authors concluded that in nonrandomized studies the risk
of gastric cancer development was significantly reduced by
*H. pylori* eradication (OR 0.23), whereas in the large and
best conducted randomized studies of *H. pylori* eradication
the ORs were much less impressive (0.67) and not statisti-
cally significant, owing to wide confidence intervals. The
authors concluded very reasonably that ‘*H. pylori* eradication
is a plausible intervention for gastric cancer prevention;
however, it seems to be relevant in only a subset of
subjects’. This was also the feeling of the authors of the
recently published Maastricht III Consensus Report [12], who
stated at the consensus meeting held in 2005 that ‘the
optimum time to eradicate *H. pylori* is before preneoplastic
lesions (atrophy, intestinal metaplasia) are present’. Anoth
Another important conclusion from the Maastricht III
consensus was that ‘the potential for gastric cancer prevention on a global scale is restricted by currently available therapies’.

Micronutrients and other chemopreventive approaches have generally been even less impressive than *H. pylori* eradication. Is there a role for pharmacologic intervention? Two reports published this year provide a mixed picture of the effects of selective COX-2 inhibitors. Yang et al. [13] took multiple gastric biopsies from Taiwanese dyspeptic patients, approximately half of whom were chronic users of celecoxib. From the initial 366 patients, 103 were found to have *H. pylori* infection with intestinal metaplasia and received *H. pylori* eradication therapy. At the initial endoscopy, the prevalence of intestinal metaplasia was similar between the chronic celecoxib users and the controls, but after a year the chronic celecoxib users appeared to have less intestinal metaplasia than those who did not take this drug. The authors speculated that celecoxib may be beneficial along with *H. pylori* eradication in the prevention of gastric cancer. Leung et al. [14] addressed this issue with rofecoxib 25 mg daily in a randomized prospective placebo-controlled trial in 213 subjects with intestinal metaplasia. After 2 years absolutely no differences in the amount or severity of intestinal metaplasia, apoptotic, or proliferative scores were found between rofecoxib and placebo. This latter study provides no optimism for COX-2 inhibitor chemoprevention in the prevention of gastric cancer, especially in view of the large cloud that hangs over all selective COX-2 inhibitors related to increased cardiovascular side-effects [15].

**Mechanisms of Gastric Carcinogenesis**

Several very interesting articles were published on the pathogenesis of *H. pylori* infection and its relationship to gastric carcinogenesis. Detailed microscopic studies of gastric biopsies from patients with dyspepsia and gastric cancer have resuscitated the idea that *H. pylori* may be invasive. While intracellular *H. pylori* has been noted repeatedly in coculture, the dogma has been that *H. pylori* does not invade gastric epithelial cells in vivo. However, recent findings that *H. pylori* may modulate the expression and functions of junctional proteins encouraged Necchi et al. to re-evaluate this dogma [16]. Using transmission electron microscopy and immunogold labeling with a variety of antibodies against *H. pylori*, lysates, and purified proteins (including VacA and CagA), *H. pylori* bacteria were identified inside the cytoplasm of epithelial cells, between epithelial cells and in the underlying lamina propria, often close to immune cells, and occasionally inside blood vessels. These findings were evident in normal mucosa, intestinal metaplasia, and in nine of 20 gastric cancers. This study of a small number of patients will undoubtedly reignite the long-simmering controversy regarding whether *H. pylori* should be regarded as invasive, especially as *H. pylori* may invade murine gastric progenitor cells [17].

Equally controversial has been the suggestion that *H. pylori* is directly mutagenic, over and above the potential mutagenicity of the accompanying inflammatory response. While chronic coculture of the AGS gastric cancer cell line with *H. pylori* led to increased mutations in the gastric epithelial cell line, in association with reduced expression of two proteins, hMLH1 and hMSH2 that are critical for DNA repair and DNA fidelity [18], it is feasible that these results could be explained by the selection pressure of *H. pylori* leading to the emergence of a previously under-represented cell population. However, in support of a directly mutagenic action in coculture, *H. pylori* was reported to induce aberrant expression of activation-induced cytidine deaminase (AID), a protein acting as a DNA and RNA editing enzyme, with the consequent accumulation of mutations in the p53 tumor suppressor gene [19]. This appears to be mediated through IkB kinase-dependent NF-kB activation and the Cag pathogenicity island, and was relatively specific for p53, with mutations occurring much less frequently in beta catenin and c-myc. Increased AID expression was also noted in *H. pylori*-infected human gastric biopsies and was decreased following *H. pylori* eradication. AID levels were elevated in gastric cancer, and similar up-regulation was seen in a mouse model of *H. pylori* infection although this did not lead to the accumulation of p53 mutations, even after 40 weeks infection. Nevertheless, owing to the frequency of p53 mutations in human gastric cancer this study provides an important potential mechanism by which chronic *H. pylori* leads to the aberrant expression of a protein involved in nucleic acid editing and somehow specifically to p53 mutation.

Genomic and proteomic technologies continue to be applied to explore *H. pylori* pathogenesis in relation to human gastric carcinogenesis. Following their important work defining the genomic changes induced by *H. pylori* in transgenic mouse models [20], Gordon’s laboratory has now turned its attention to humans. In a prior publication [17], this group reported an *H. pylori* isolate from a patient with chronic atrophic gastritis that appeared to bind and persist within gastric stem cells. Customized Affymetrix gene chips representing the genome of this strain were then synthesized and used for genotyping other *H. pylori* isolates from chronic gastritis patients. By combining genomic expression data with extensive clinical follow up, this impressive publication describes the genetic signature of *H. pylori* that may determine progression to cancer in these patients, genes regulated by acid during in vitro growth, and document gene defines clusters expressed during the adaptation of *H. pylori* to growth in the achlorhydric stomach. Ellmark et al. [21] constructed
large-scale antibody microarrays with 127 antibodies against antigens thought to be important in immunoregulation, to assess simultaneously the expression of multiple antigens in *H. pylori*-positive and -negative gastric cancers compared with their ‘normal’ resection margins (the *H. pylori*-negative cases were obtained from pancreatic cancer patients). Both tumor-associated signatures and *H. pylori* infection-associated signatures were obtained after mathematical correction and clustering. In a summary Venn diagram, specific proteins in each of these categories were evident and only one protein (the complement subunit C1s) was exclusively expressed in *H. pylori*-infected gastric tissues but not in tumors. Lin et al. [22] also used a proteomic approach to identify serum antibodies recognizing specific *H. pylori* antigens present in strains from patients with gastric cancer but not present in patients infected by duodenal ulcer-associated strains. The most promising differentially recognized antigen of the gastric cancer-associated strains was the chaperonin GroES (recognized by 64% of gastric cancer serum samples, compared with 31% of the gastritis samples and 35% of the samples from duodenal ulcer patients). Recombinant GroES was synthesized and in vitro strongly stimulated interleukins (IL) 8 and 6, granulocyte macrophage colony-stimulating factor, IL-1β, tumor necrosis factor α (TNF-α), cyclooxygenase 2, and prostaglandin E2 expression from peripheral blood monocytes. Moreover in gastric epithelial cells, GroES-up-regulated IL-8, c-Jun, c-Fos and cyclin D1 increased cell proliferation and decreased p27 expression. Many of these effects had been observed with whole *H. pylori* and are thought to be important in the pathogenesis of gastric cancer, as they are similarly regulated in vivo. It is noteworthy that this study using very large numbers of clinical samples, careful proteomic analysis, and in vitro verification to support the biologic significance of their findings clearly illustrates the power of proteomic technology to identify potentially important *H. pylori* proteins. Identifying candidate virulence factors expressed by gastric cancer-causing strains but not duodenal ulcer strains has been a major challenge previously.

Following the adherence of *H. pylori* to gastric epithelial cell lines, extensive arrays of downstream signaling pathways resulting in potentially pro-carcinogenic events have been described, many of which are dependent on an intact type IV secretion system. To these effects can now be added increased cellular invasion, a hallmark of increased malignancy of cells in culture [23]. This effect was not related to VacA but required both direct contact and activation of the c-Met receptor, accompanied by increased activity of the matrix metalloproteinases MMP2 and MMP9. Whether similar events occur in vivo remains to be determined. In vivo *H. pylori* stimulates the production of macrophage migration inhibitory factor (MIF) from several cell types. Beswick et al. showed that the production of MIF by gastric epithelial cell lines was dependent on CagA, that MIF binds to CD74 (the class II MHC-associated invariant chain) to promote epithelial proliferation and to decrease apoptosis, and that this was associated with decreased p53 phosphorylation and increased Bcl-2 expression [24].

Moving from studies in cell lines to the evaluation of molecular changes in human gastric cancer tissues, Griffiths et al. reported increased expression of hypoxia-inducible factor (HIF) 1α with progression through the normal-*H. pylori* gastritis-intestinal metaplasia-dysplasia-carcinoma sequence [25]. Furthermore, increased HIF 1α expression was associated with the worst prognosis in a large series of gastric and esophageal cancer cases, though this was true only in univariate analysis. These results are consistent with reports of increased HIF 1α expression in some other malignancies. RUNX3 is a transcription factor that was proposed to act as a gastric cancer tumor suppressor in a high profile publication by Li et al. in 2002 [26]. However, some other groups could not confirm an abnormal gastric phenotype in RUNX3 knockout mice, nor did the mice develop gastric cancer. To further investigate the importance of gastric epithelial expression of RUNX3, Friedrich et al. [27] examined RUNX3 expression by immunohistochemistry, laser capture microdissection, and quantitative PCR and reported that the level of RUNX3 in gastric epithelium was very low and not influenced by *H. pylori* or the development of gastric cancer. Furthermore, RUNX3 was mainly expressed in the gastric mucosa by infiltrating inflammatory cells rather than epithelial cells, adding further uncertainty over RUNX3 as a gastric cancer tumor suppressor.

The association of *H. pylori* infection with gene methylation has provided another possible mechanistic link between chronic *H. pylori* colonization and gastric carcinogenesis. Of multiple genes targeted by *H. pylori*, E-cadherin is of great interest because it is frequently down-regulated in sporadic gastric cancer, germline mutations in E-cadherin are associated with the hereditary diffuse cancer syndrome, and the effects of E-cadherin down-regulation includes loss of tight junction function and dysregulation of cell proliferation. Of 28 *H. pylori*-infected dyspeptic patients studied in Hong Kong [28], over half had E-cadherin methylation. This was significantly decreased 1 year after *H. pylori* eradication, suggesting that E-cadherin methylation may be reversed with eradication of the organism and resolution of gastric inflammation. However, methylation status may be unrelated to *H. pylori* since even in individuals without any evidence of *H. pylori* infection, gastric cancer cases had increased methylation of promoters in multiple genes, especially in patients with multiple gastric cancers [29].
Host Genetic Polymorphisms and Cancer Susceptibility

The landmark publication of El-Omar et al. linking polymorphisms in genes regulating the gastric inflammatory responses to gastric cancer risk from *H. pylori* has spurred many groups worldwide to investigate other susceptibility loci governed by polymorphic alleles, particularly those of the innate immune response. The pathogen-associated intracellular recognition molecules NOD1 and NOD2 have recently emerged as potentially important regulators of chronic inflammatory conditions. NOD2 mutations segregate with particular phenotypes of Crohn’s disease and NOD1 appears to be involved in the activation of a key transcription factor, NF-kB, by the *Cag* pathogenicity island [31]. Rosenstiel et al. reported that NOD1 and NOD2 were up-regulated in the gastric epithelial cells of patients with chronic *H. pylori* infection and that the Crohn’s disease-associated NOD2 variant R702W was significantly more prevalent in patients with gastric lymphoma than in *H. pylori*-infected individuals with gastritis or gastric ulcers [32]. No similar correlation between genetic variants of NOD1 was found and gastric cancer was not addressed in this study. Cyclooxygenase2 (COX-2) has long been known to be over-expressed in gastric cancers and in *H. pylori* infection. In a large series of gastric cancer cases and controls with preneoplastic lesions from China, Liu et al. reported an association between specific COX-2 genotypes associated with high level COX-2 expression and gastric cancer risk [33]. However, they did not state whether this association holds true after adjusting for other known gastric cancer-associated polymorphisms such as IL-1β and TNF-α.

Screening the genotype distribution and allele frequencies of single nucleotide polymorphisms of four matrix metalloproteinases and two tissue inhibitors of matrix metalloproteinases, Kubben et al. reported that a single allele of MMP-7 was associated with *H. pylori* status and prognosis in Dutch gastric cancer patients, while a polymorphism of TIMP-2 correlates with tumor-related survival [34]. Again, previously described polymorphisms were not adjusted for, and the data require verification in other populations. Toll-like receptor 4 (TLR-4) is a receptor for lipopolysaccharide and may be important for *H. pylori* signaling to macrophages, monocytes, and perhaps also gastric epithelial cells. TLR-4 polymorphisms and mutations have been associated with a variety of inflammatory conditions, where defective signaling through TLR-4 is thought to be responsible for activating an exaggerated and inappropriate inflammatory response. Hold et al. addressed this issue with respect to *H. pylori* infection in gastric carcinogenesis [35]. A large series of patients previously investigated for cytokine polymorphisms and susceptibility to gastric cancer from Poland, gastric cancer cases and their achlorhydric family member controls from Scotland, and cases of gastric and esophageal cancer from a US cancer registry were all tested for TLR-4 polymorphisms. An association between a polymorphism in TLR-4 that renders cells hyporesponsive to LPS and an increased risk of noncardia gastric cancer and its precursor lesions including achlorhydria was subsequently identified. This association was specific for noncardia gastric cancer (it was not observed in esophageal or gastric cardia cases) and remained even after correcting for the polymorphic variations in IL-1β and the IL-1 receptor previously documented by this group, although whether it remains after correction for all other cytokine polymorphisms was not stated in the article.

MALT Lymphoma

That *H. pylori* eradication is a definitive cure of low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma has found worldwide recognition and appreciation. The most recent study from Korea reports a median time of 3 months for reaching complete remission in 84 of 99 patients following successful *H. pylori* eradication and a long-term complete remission in 94% of those [36]. Tumors located in the distal stomach had a more favorable response than those in the proximal stomach [36].

In another study, a group of 90 *H. pylori*-infected patients with low-grade MALT lymphoma underwent eradication therapy for 14 days and 85 (94.4%) reached complete remission. Median follow-up period after complete remission was 45 months (range 15–109). Only eight (10.4%) patients were found with recurrence of MALT lymphoma. Cumulative recurrence rates were 2.7, 11.5, and 12.2% at 1, 2, and 3 years respectively. Persistence of *H. pylori* was identified as the most important risk factor involved in recurrence, and therefore an adequate eradication regimen and accurate regular evaluations for *H. pylori* status are needed during follow up of primary gastric low-grade MALT lymphoma [37].

Long-term follow up of patients with MALT lymphoma is recommended as it is also possible that a metachromous gastric cancer can be detected [38]. It is also not unusual for *H. pylori* to be associated with extragastric locations such as reported for primary orbital lymphoma [39].

Some peculiar aspects in the therapy of MALT lymphomas are that some patients respond to therapy even in the absence of detectable *H. pylori*, as well as others with *H. pylori*-associated extragastric MALT lymphomas [40,41].

Carrier of the rare allele T have more than doubled risk of developing lymphoma than controls. *H. pylori*-induced up-regulation of NOD1 and NOD2 in vivo may play a critical
role in the recognition of this common pathogen. A missense mutation in the leucine-rich region of NOD2 is associated with increased risk of gastric lymphoma [32,42].

Low levels of *H. pylori* infection as they occur in vivo are associated with B-cell survival and proliferation, consistent with their potential to evolve into MALT lymphoma [43].

CagA, like interleukin-3, can enhance lymphocytes ability to evade apoptosis through phosphorylation of Bad. This may account, at least in part, for the direct ability of CagA to promote lymphomagenesis [44].

Two insightful reviews dealt with the management of gastric MALT lymphoma in great detail [45,46], including the basic mechanisms involved in the pathogenesis of MALT lymphoma. A genetic link of CTLA4 gene polymorphisms with development of gastric MALT lymphoma has been identified which further supports the fundamental role of host-activated T cells in MALT lymphomagenesis [47]. Almost 100% of C57BL/6 mice infected with *H. heilmanii* developed gastric MALT lymphoma after a 6-month period and lymphatic neoplasia was associated with destruction of parietal cells [48]. Genetic variations as predisposing factors of primary gastric B-cell lymphoma development have been excluded in a study from Germany [49]. Different clonality is a common reason for the differential response of coexisting low-grade and high-grade MALT lymphoma to *H. pylori* eradication therapy. The immunohistochemical examination of BCL10 expression may help to identify the coexistence of these components [50].

T(11;18)/API2-MALT1 translocation is frequent, while IGH-involved translocation is rare in gastric MALT lymphoma in Japan. This may have important impact on the clinical outcome [51].

Interestingly, γ-glutamyl transpeptidase has been reported as a novel immunosuppressive factor produced by *H. pylori* that inhibits regulatory T-cell proliferation by induction of a cell cycle arrest in the G(1) phase [52].

Gastric MALT lymphoma is an interesting human and experimental model that will continue to give us important insights into the specific and general principles neoplasia development.

**H. pylori** and Breast Cancer?

Advances in animal models of *Helicobacter* infection relevant to gastric carcinogenesis were few in the past year. However, during investigations of the intestinal bacterial flora in relationship to colon cancer in the APC/Min mouse model, Rao et al. found that orogastric administration of the murine intestinal species *Helicobacter hepaticus* increased not only the number of intestinal tumors but also breast cancers in susceptible strains of female mice [53]. Further experiments demonstrated that this was dependent on TNF-α and the absence of a specific subset of regulatory T cells. These intriguing experiments led the authors to postulate that gastrointestinal microbial infection by *Helicobacter* species and related organisms may dysregulate systemic immune responses, resulting in cancers in anatomically unrelated sites such as the breast. If true in humans, then perhaps breast cancer could one day be screened for through examining the stool rather than imaging the breasts!

**Conflicts of interest**

The authors have declared no conflicts of interest.

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