Chapter 2
Infection Based Gastric Cancer

Lydia E. Wroblewski and Richard M. Peek Jr.

Abstract Gastric cancer is one of the leading causes of cancer-related death in the world. *Helicobacter pylori* is currently the strongest known risk factor for this disease and is classified as a type I carcinogen by the World Health Organization. Many factors play a role in the progression towards gastric cancer including, but not limited to, bacterial virulence factors, host genetics, diet, and the gastric microbiota. The stomach, once thought to be a sterile environment, is now known to host a rich microbiota, which is unique to each individual. A complex interplay exists between *H. pylori* and the gastric microbiota which may one day become a target for personalized medicine to attenuate the progression towards gastric cancer. In this chapter, we discuss how the infectious bacterium, *H. pylori*, interacts with its host to augment the risk of developing gastric cancer.

Keywords *Helicobacter pylori* · Gastric cancer · Microbiota · Infectious agent

2.1 Infection-Associated Cancers

Infectious agents are major contributors to the development of human cancer and collectively they impose a large burden on global health. In 2008, two million of an estimated 12.7 million new cases of cancer were ascribed to infections. Perhaps not surprisingly, 80% of these infection-based cancers occurred in less developed regions of the world, which is likely attributable to a inadequate preventative treatment of infectious agents [1].

Francis Peyton Rous first noted the association between infection with specific pathogens and cancer over a century ago in 1911 when he demonstrated that a malignant tumor (a sarcoma in chickens) was transmissible. This is now known as the Rous sarcoma virus and its pathogenesis is still widely studied over 100 years from its discovery [2]. In 2012, the International Agency for Research on Cancer

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Table 2.1 Group 1 infectious agents and the major cancer sites they are associated with

Cancer site	Infectious agent
Stomach	*H. pylori*, EBV
Liver	HBC, HCV, *Opisthorchis viverrini*, *Clonorchis sinensis*
Cervix	HPV
Anogenital	HPV
Nasopharynx	EBV
Oropharynx	HPV
Kaposi's sarcoma	Human herpes virus type 8
Non-Hodgkin lymphoma	*H. pylori*, EBV, HCV, human T-cell lymphotropic virus type 1
Hodgkin's lymphoma	EBV
Bladder	*Schistosoma haematobium*

(IARC) classified eleven infectious agents as harboring carcinogenic potential for humans [1, 3]. These include *H. pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), *Opisthorchis viverrini*, *Clonorchis sinensis*, human papillomavirus (HPV), Epstein-Barr virus (EBV), human T-cell lymphotropic virus type 1 (HTLV-1), Merkel Cell polyoma virus (MCPv), human herpes virus type 8 (HHV-8; also known as Kaposi's sarcoma herpes virus KSHV), and *Schistosoma haematobium*. The cancers these infectious agents are associated with include, but are not limited to, gastric, liver, cervical and bladder, and are summarized in Table 2.1.

One of the primary infectious agents deemed a class I carcinogen is *H. pylori*. This single bacterium accounts for a staggering 32.5% of the two million new cancer cases attributable to infections worldwide occurring in 2008 [1]. To date, *H. pylori* is the only bacterium that is recognized as causally being associated with malignant neoplasia in humans and it confers an attributable risk of approximately 89% for non-cardia gastric carcinoma which translates to around 780,000 new gastric cancer cases, emphasizing the role of *H. pylori* as a major cause of cancer [4].

2.2 Gastric Cancer

Gastric cancer was the leading cause of cancer-related death in the developed world until the mid-1930s and despite a significant decrease in incidence rates, gastric cancer is still the third leading cause of cancer-related death in the world, resulting in close to 740,000 deaths in 2008. Within the United States the 5-year survival rate is surprisingly low, at less than 15% [1, 5–7]; such high mortality rates are primarily thought to be due to late-stage detection.

The incidence and mortality rates of gastric adenocarcinoma in developed countries have declined significantly over the past century. This is primarily attributed to a decline in intestinal-type adenocarcinomas in the distal stomach and may be related to decreased transmission of *H. pylori* in childhood following improved

hygiene and smaller family units and/or changes in food preservation and storage [6, 8, 9]. Distal gastric adenocarcinomas are strongly associated with *H. pylori* infection, but the causal relationship between *H. pylori* and gastric cardia adenocarcinomas is less well defined. Conversely, the incidence rates of cancers localized to the cardia, as well as Barrett's esophagus and adenocarcinomas originating in the gastroesophageal junction, have been increasing in both the United States and Europe. This increase is seen predominately in white males and to date the reasons for this increase are unclear [9–11].

The Cancer Genome Atlas (TCGA) research network proposed a new molecular classification whereby gastric cancer is divided into four subtypes and EBV-associated gastric tumors have been classified as a newly distinct subtype of gastric cancer; EBV-positive tumors [12]. The three other subtypes of gastric cancer are termed microsatellite-instable tumors, genomically stable tumors, and tumors with chromosomal instability. EBV-positive tumors contain *PIK3CA* mutations, DNA hypermethylation, and increased expression of *JAK2*, *CD274*, and *PDCD1LG2* [12].

Adenocarcinoma is the most common type of cancer affecting the stomach, but lymphoma and leiomyosarcoma may also occur. Distinct variants of gastric adenocarcinoma can be separated into two types which may be differentiated histologically; intestinal-type adenocarcinoma, which progresses through a series of well-defined histological steps and diffuse-type gastric cancer, which consists of individually infiltrating neoplastic cells that do not form glandular structures [13].

The strongest identified risk factor for developing gastric adenocarcinoma is chronic infection with *H. pylori* and whilst most human gastric cancers arise following long-term infection with *H. pylori*, emerging data suggest that other components of the gastric microbiota may also influence gastric disease progression (see Sect. 2.3.5). The reported degree to which *H. pylori* increases the risk for gastric adenocarcinoma varies between studies and is likely dependent on several factors including patient age, selection of controls, and the site and stage of gastric cancer. In one study, infection with *H. pylori* was associated with 6.2% of all gastric cancers [4]. In another study, the combined incidence of intestinal and diffuse-type gastric cancer in *H. pylori*-infected individuals was reported to be approximately 3%, compared with 0% in uninfected persons [14]. As our knowledge currently stands, it is not possible to predict which infected individuals will develop gastric cancer and what form this will take.

2.3 Factors That Influence Gastric Carcinogenesis

2.3.1 Host Genetics

The combination of a more virulent strain of *H. pylori* infecting genetically susceptible hosts further increases the risk of developing gastric cancer. For example, infection with *H. pylori* increases gastric mucosal expression of the pro-inflammatory

cytokine, IL-1ß. Individuals who possess polymorphisms in IL-1ß that culminate in high expression levels are at a significantly higher risk of developing distal gastric adenocarcinoma compared to individuals with genotypes that limit IL-1ß expression, but only when colonized with *H. pylori* [15]. Further, the combination of colonization with *H. pylori cagA*$^+$ or *vacA* s1-type strains (discussed further in *H. pylori* section 2.3.3) in conjunction with high-expressing IL-1ß polymorphisms on the host side, confers a 25- or 87-fold increase in risk, respectively, for developing gastric cancer compared to uninfected individuals [16]. Polymorphisms that increase expression of the pro-inflammatory cytokines TNF-α and Il-10 are also associated with an augmentation in risk of developing gastric cancer and its precursors in the presence of *H. pylori* [17].

2.3.2 The Environment

Case-control studies have identified clear associations between diet and the risk of developing gastric cancer. Diets rich in fruits and vegetables and therefore antioxidants are protective against gastric cancer. Conversely, diets containing a high amount of salted, pickled, smoked or poorly preserved foods, diets rich in meat which induces production of nitrosamines, and those with low fruit and vegetable content are most commonly associated with an increased risk for developing gastric cancer [18–24].

When *H. pylori* is present, high dietary salt intake and low iron levels are highly associated with an increased risk for developing gastric cancer [25–27]. In animal models, high salt diets have been reported to increase expression of the *H. pylori* virulence factors CagA, VacA and UreA [28–30]. Similarly, iron deficiency in *H. pylori*-infected persons is also thought to accelerate the development of carcinogenesis by increasing the virulence potential of *H. pylori* [26].

2.3.3 Infectious Agents

2.3.3.1 *H. pylori*

H. pylori is a epsilonproteobacterium and a member of the *Helicobacteraceae* family that selectively colonizes gastric epithelium. *H. pylori* has colonized humans for around 60,000 years; infection is usually acquired in childhood and in the absence of combined antibiotic therapy, can persist for the life time of the host [31]. This long standing relationship between *H. pylori* and its human host, combined with approximately half of the world's population currently being colonized with *H. pylori* has driven many investigators to try and define specific mechanisms through which *H. pylori* interacts with humans and induces disease [32].

2.3.3.2 *H. pylori* Virulence Factors

H. pylori virulence factors play a key role in determining the risk of developing gastric cancer. One *H. pylori* pathogenic constituent that is linked to carcinogenicity is the *cag* pathogenicity island (*cag*PAI), which contains a cluster of genes encoding proteins that form a type IV bacterial secretion system (T4SS). The *cag* T4SS translocates CagA from adherent *H. pylori* across the bacterial and epithelial membranes into host cells. Around 60% of *H. pylori* isolates from Western countries contain the *cag*PAI and almost all strains from East Asia are positive for *cag*PAI [33–36]. Infection with *cagA*-positive *H. pylori* strains has been associated with developing intestinal and diffuse gastric adenocarcinoma at 2–3 times the frequency of those infected with *H. pylori* strains that are *cagA*-negative [37, 38].

CagA exists in alternative structures and contains different glutamate-proline-isoleucine-tyrosine-alanine (EPIYA) motifs, which may also be used as indicators of pathologic outcome [39–41]. Four different EPIYA motifs (EPIYA-A, -B, -C, or -D) have been identified [39–41]. EPIYA-A and EPIYA-B motifs are found in most strains, while the EPIYA-C motif is predominately found in Western strains and the number of EPIYA-C sites is associated with an elevated risk of developing gastric cancer [42]. Strains that contain the EPIYA-D motif are typically East Asian strains and are associated with increased pathogenesis compared with strains harboring C-type CagA motifs (Fig. 2.1) [39, 43]. Following translocation, CagA is tyrosine

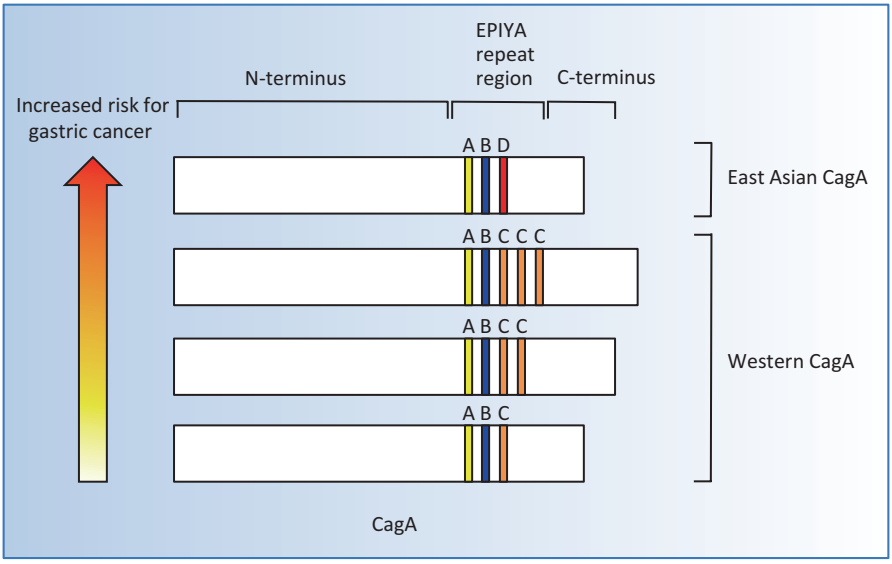

Fig. 2.1 Schematic representation of CagA EPIYA motifs. EPIYA motifs are sites of tyrosine phosphorylation. EPIYA-D motifs are commonly found in East Asian CagA sequences, EPIYA-C motifs are generally found in Western CagA sequences and EPIYA-A and EPIYA-B motifs are found in most strains. EPIYA motifs can be used to predict pathologic outcome, with EPIYA-D motifs associated with increased pathogenesis compared to a single EPIYA-C motif

phosphorylated at EPIYA motifs and can induce cellular response with carcinogenic potential. Non-phosphorylated CagA also exerts effects within host cells that contribute to pathogenesis. Unmodified CagA targets many cellular effectors including apical-junctional components, the hepatocyte growth factor receptor c-Met, the phospholipase PLC-γ, the adaptor protein Grb2, and the kinase PAR1b/MARK2, leading to pro-inflammatory and mitogenic responses, disruption of cell-cell junctions, and loss of cellular polarity [44–51]. Independent of CagA, *H. pylori* can also induce mislocalization of the tight junction proteins occludin and claudin-7 and alter barrier function [52, 53].

Another widely studied *H. pylori* virulence factor is the multifunctional cytotoxin VacA which causes vacuolation, altered plasma and mitochondrial membrane permeability, autophagy, and apoptosis [54, 55]. The *vacA* gene is found in all strains of *H. pylori*, and contains a number of variable loci in the 5′ region of the gene termed s, i and m regions. This 5′ terminus encodes the signal sequence and amino-terminus of the secreted toxin (allele types s1a, s1b, s1c, or s2), an intermediate region (allele types i1 or i2), and a mid-region (allele types m1 or m2) [56, 57]. Strains containing type s1, i1, or m1 alleles are highly associated with gastric cancer [56, 58, 59] and are associated with a greater risk of developing gastric cancer than *cag* status [57, 60, 61]. VacA and CagA may also counter-regulate each other's actions to manipulate host cell responses [62–64].

Blood group antigen binding adhesin (BabA) and Sialic acid-binding adhesin (SabA) are two other important *H. pylori* constituents that have been linked to the development of gastric cancer [65]. BabA is an outer membrane protein that binds to fucosylated Lewis^b antigen (Le^b) on the surface of gastric epithelial cells [65–68]. The presence of *babA2,* the gene encoding BabA*,* is associated with gastric cancer [65], and BabA expression is linked with adenocarcinoma of the gastric cardia [69]. The combined effect of BabA with *cagA* and *vacA* s1 alleles is strongly linked to a more severe gastric disease outcome [65, 70]. Sialyl-Lewis^x is expressed in the gastric epithelium and expression is increased by chronic inflammation [71]. SabA binds to sialyl-Lewis^x antigen, suggesting that *H. pylori* may modulate sialyl-Lewis^x in the host to enhance attachment and colonization [72].

2.3.4 Epstein-Barr Virus (EBV)

EBV infection is another pathogen that is associated with gastric cancers. EBV-positive tumors comprise almost 10% of gastric cancers, are associated with extensive gene methylation, predominately affect males, and tumors are generally located in the cardia or corpus, and are less frequently found in the antrum [73, 74]. EBV and *H. pylori* may act synergistically in the gastric epithelium to promote the progression towards gastric cancer and the majority of EBV-positive individuals are also co-positive for *H. pylori* [75]. A case-control study has shown that the combination of EBV and *H. pylori* induces severe inflammation and, in this way, augments the risk of developing intestinal type gastric cancer [76]. A meta-analysis

with meta-regression to control for heterogeneity across studies also supported the notion that infection with EBV increases the risk of developing gastric cancer [77]. In a recent mechanistic study, EBV was shown to methylate the phosphatase SHP1 and thereby prevent SHP1 from dephosphorylating CagA. This perturbation increases the oncogenic activity of CagA and may increase the synergistic effect of EBV and *H. pylori* [78].

It has been shown that patients who present with the highest levels of antibodies against EBV and *H. pylori* also express the highest levels of immune cell infiltration, and are therefore, at increased risk for developing more severe inflammation. In a recent cross-sectional study of 127 patients with gastric cancer, the presence of elevated serum levels of the cytokine interferon-gamma (IFN-γ) has been associated with EBV reactivation and intestinal gastric cancer. However, IFN-γ can exert both pro-inflammatory and anti-inflammatory effects, and further studies need to be conducted to determine if IFN-γ is acting to repress EBV activity or is augmenting EBV and *H. pylori*-induced gastric cancer progression [79].

2.3.5 The Human Gastric Microbiome

The gut microbiota is essential to maintain host physiology through its integral role in cellular metabolism, nutrient absorption and immune defense against invading pathogens. When the microbiota is altered, homeostasis is also disrupted, and diseases may develop. Historically, research has focused on a single organism causing disease, for example *H. pylori* and gastric cancer; however, a rapid burst in molecular technologies such as next-generation sequencing in combination with computational analysis and new and well-designed animal models have transformed our understanding of how the microbiota is associated with disease states. A diverse bacterial community is found within the stomach with colonization densities reported to range from between 10^1 and 10^3 colony forming units/g [80]. Emerging data strongly suggest that the gastric microbiota affects gastric homeostasis in combination with *H. pylori* infection [81].

The gastric microbiota in *H. pylori*-negative individuals is highly diverse. Through one sequencing study, 128 phylotypes were identified within eight bacterial phyla; and the five most abundant phyla were Proteobacteria, Firmicutes, Bacteroidetes, Fusobacteria, and Actinobacteria [82, 83]. In an independent study using tagged 454 pyrosequencing analysis, 262 phylotypes representing 13 phyla were identified in gastric biopsies from *H. pylori*-negative persons [84]. Even though the results of the analysis vary depending on the sequencing approach and sample preparation, in addition to the large variability between the microbiota in different individuals, it is clear that the gastric microbiota is highly diverse [82, 84]. In stark contrast, in *H. pylori* infected individuals, *H. pylori* was found to be the single most abundant phylotype present in the stomach and accounts for between 72% and 97% of all sequence reads [82, 84, 85].

Currently there are very few studies that have examined differences in microbial composition and outcomes stratified by disease. Atrophic gastritis is a key step in the histologic progression to intestinal-type gastric cancer and predisposes the stomach to elevated pH [13]. The hypochlorhydric environment found in atrophic gastritis permits colonization of other bacteria that may enter the stomach and may further promote the progression towards gastric cancer. In one study, the microbiota of patients with gastric cancer was found to be equally as complex as the microbiota of dysplastic patients with five predominant bacterial phyla identified in both groups; Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria. *H. pylori* was detected in relatively low abundance and the microbiota was instead dominated by species of *Streptococcus*, *Lactobacillus*, *Veillonella*, and *Prevotella* [86]. A more recent study using pyrosequencing found distinct differences when the gastric microbiota was compared in different disease stages from chronic gastritis, to intestinal metaplasia and gastric cancer. In gastric cancer, the Bacilli class and Streptococcaceae family were significantly increased compared to what was found in chronic gastritis and intestinal metaplasia, where the Epsilonproteobacteria class and Helicobacteraceae family were both decreased [87]. In a recent large study, the gastric microbiota was compared in chronic gastritis and gastric cancer and significant differences were identified between the two groups. Specifically, the microbiota in gastric cancer had decreased diversity, reduced *Helicobacter* abundance and over-abundance of *Citrobacter*, *Clostridium*, *Lactobacillus*, *Achromobacter* and *Rhodococcus*, which are usually found in the intestinal microbiota [88].

These studies are intriguing and demonstrate associations between the human gastric microbiota and *H. pylori* with gastric disease, however, they are not able to differentiate between cause and effect. To start to address whether changes in the gastric microbiota play a direct role in the development of gastric cancer, or are secondary to the changing gastric environment, further detailed molecular studies to define the composition of the gastric microbiota in well-characterized human populations, with and without gastric cancer will need to be conducted. As of now, infection with *H. pylori* is the strongest known risk factor for developing gastric cancer, however, a large longitudinal human study suggests that other components of the gastric microbiota may influence gastric disease progression. In a 15-year follow-up study of 3365 subjects, antibiotic treatment of *H. pylori* infection significantly reduced the incidence of gastric cancer despite less than half of the treated individuals remaining free of *H. pylori* infection. The incidence of gastric cancer was decreased to a similar level in individuals that remained free of *H. pylori* over 15 years versus those where eradication was not successful, suggesting that treatment with antibiotics may modify the microbiota in such a way that the development of gastric cancer is attenuated despite the presence of *H. pylori* [89]. Along similar lines, computational analysis of bacterial DNA within known cancer genomes determined that gastric adenocarcinoma contained the second highest number of bacterial DNA sequences. Interestingly, this bacterial DNA was not *H. pylori*, but was instead, *Pseudomonas* [90].

2.3.6 The Rodent Gastric Microbiome

Animal models greatly increase our ability to establish causality. Inbred mice with defined genotypes are frequently used as a model of gastric carcinogenesis and transgenic mice can be generated to allow for in-depth analyses of host responses.

Similar to in the human stomach, the phylotypes with the most members in the mouse gastric environment are *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, and *Actinobacteria* [91]. Similar to in humans, *H. pylori* induces chronic atrophic gastritis in the mouse gastric mucosa; however, *Acinetobacter lwoffii* in the absence of *H. pylori* can also induce gastric inflammation and metaplastic changes comparable to that induced by *H. pylori* [92]. Also, the extent to which inflammation is induced by *H. pylori* can vary depending on the composition of the mouse gastric microbiota with different ratios of *Lactobacillus* species ASF360 and ASF361 altering the outcome for the inflammation and injury responses when mice were subsequently challenged with *H. pylori* [91].

Gnotobiotic mice provide a powerful model in which the microbiota can be carefully controlled by incremental addition of individual or collections of microorganisms. INS-GAS mice are transgenic hypergastrinemic mice that, in the presence of a complex gastric microbiota, spontaneously develop gastric cancer [93, 94]. However, development of gastric cancer was delayed by over a year in gnotobiotic INS-GAS mice [95]. In the context of *H. pylori* infection, gnotobiotic mice challenged with *H. pylori* developed less severe lesions and were slower to develop gastric cancer than *H. pylori*-infected INS-GAS mice with a complex microbiota [95]. Subsequent work has shown that a microbiota containing only three species of commensal bacteria (ASF356 *Clostridium* species, ASF361 *Lactobacillus murinus* and ASF519 *Bacteroides species*) was sufficient to promote gastric cancer in *H. pylori*-infected INS-GAS mice to the same extent as what was seen in *H. pylori*-infected INS-GAS mice with a complex microbiota [96].

Extragastric constituents of the microbiota may also influence outcomes of *H. pylori*-induced gastric cancer in mice. Co-infection of mice with the intestinal *Helicobacter* species *H. bilis* or *H. muridarum* significantly decreased *H. pylori*-induced gastric disease by altering T helper 1-type cell responses [97, 98]. However, pre-existing infection with *H. hepaticus* increased *H. pylori*-induced gastric disease through a T helper 17-type cell response to the combined infection [97]. Helminth infections may also decrease the degree to which *H. pylori*-induces changes in the microbiota of mice [99].

Although great advances are being made in understanding the complex interplay between the microbiota and *H. pylori* in the development of gastric cancer in animal models, rodent models have several limitations. Among other problems, rodents are not naturally infected with *H. pylori* and need to be experimentally infected with rodent adapted strains. Also, the topography of *H. pylori* colonization in rodent stomachs does not precisely reflect that of humans [81]. An exciting animal model for investigating interactions between *H. pylori* and the gastric microbiota is the rhesus monkey (*Macaca mulatta*). Rhesus monkeys are naturally infected early in

life with *H. pylori* strains that are indistinguishable from human strains. In addition, the rhesus monkey stomach is similar to humans, in contrast to rodents, which possess a forestomach, and gastric biopsies can be obtained over time by endoscopy [100]. Similar to humans, *Helicobacter* species formed the majority of the gastric microbiota when present in rhesus macaques [100].

2.4 Conclusions

Gastric cancer culminates in a high number of cancer-related deaths throughout the world and understanding the complex interplay between host factors, *H. pylori,* and the gastric microbiota will be critical to identify individuals who are most at risk of developing gastric cancer (Fig. 2.2). There has been some success in generating a *H. pylori* vaccine in *H. pylori* naive children [101], but eradication of *H. pylori* using antibiotics is not always successful and contributes to the global problem of bacterial resistance. Moreover, there is mounting evidence to suggest *H. pylori* may be beneficial to a large proportion of infected individuals who may be protected against esophageal diseases, gastric reflux disease and some allergic and autoimmune diseases. Thus, it is increasingly important to identify the 1–3% of individuals colonized by *H. pylori* that will develop gastric cancer and specifically test and treat these persons.

In the future, treatment for gastric cancer may soon involve personalized medicine targeting elements such as the gastric microbiota. Indeed, pioneering work

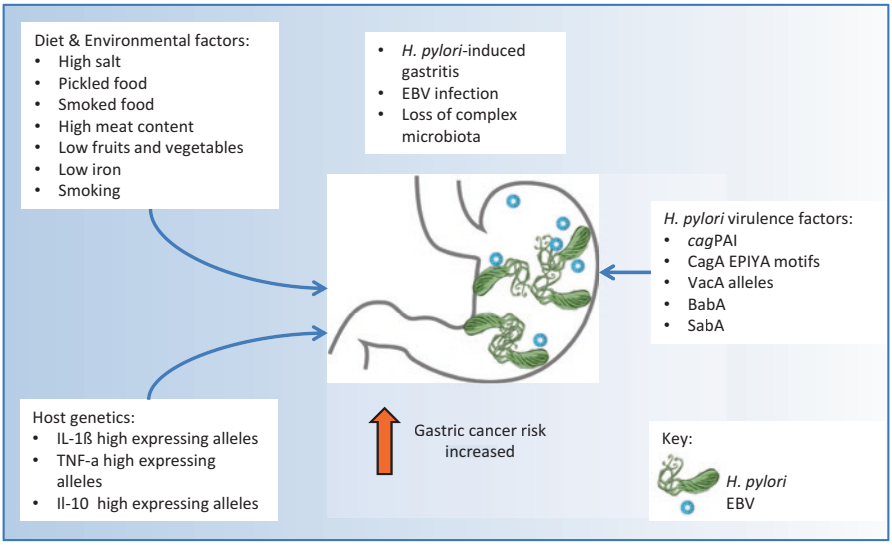

Fig. 2.2 Schematic representation of gastric cancer risk factors in combination with *H. pylori*-induced chronic gastritis

recently published has demonstrated that cancer patients have a better therapeutic outcome with PD-1 inhibitor immunotherapy when their gut microbiome is complex and intact compared to individuals who had received antibiotics that disrupted the microbiome around the time of receiving immunotherapy [102]. The hope is that we may be able to identify groups of bacterial taxa present in the stomach that are predictive of gastric disease outcome. It may also be possible to manipulate an individual's specific microbiota to produce more favorable outcomes following infection with *H. pylori*. Exploiting the microbiome to improve gastric cancer outcomes will be challenging given the large amount of variation between individuals and detailed analyses of the human gastric microbiome still need to be completed. Furthermore, it will be critical to determine cause and effect outcomes when targeting the gastric microbiome to alter disease outcome [103]. Ultimately, understanding the dynamics of the microbiota, along with host genetic and dietary factors, and *H. pylori* virulence factors will be essential to devise a plan to treat patients with precancerous gastric disease.

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