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Role of Helicobacter Pylori Infection in Development of Gastrointestinal Malignancy

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ROLE OF HELICOBACTER PYLORI INFECTION IN DEVELOPMENT OF GASTROINTESTINAL MALIGNANCY

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Introduction. Helicobacter Pylori (HP) infection has been associated with chronic inflammation of the stomach and may also be associated with the development of gastrointestinal malignancy.

Purpose of Study: This study will examine the literature related to HP infection associated with the cancers of the stomach.

Materials and Methods: A literature review was conducted on the reported research of HP infection associated with gastric cancer cases.

Results and Discussions: Helicobacter pylori is a gastric pathogen that colonizes approximately 50% of the world's population. Infection with H. pylori causes chronic inflammation and significantly increases the risk of developing duodenal and gastric ulcer disease and gastric cancer. Infection with H. pylori is the strongest known risk factor for gastric cancer, which is the second leading cause of cancer-related deaths worldwide. Once H. pylori colonizes the gastric environment, it persists for the lifetime of the host, suggesting that the host immune response is ineffective in clearing this bacterium. In this review, we discuss the host immune response and examine other host factors that increase the pathogenic potential of this bacterium, including host polymorphisms, alterations to the apical-junctional complex, and the effects of environmental factors.In addition to host effects and responses, H. pylori strains are genetically diverse. [69]

Conclusions: The exact mechanism to explain the role of H. pylori in carcinogenesis is incompletely understood. Multiple studies have demonstrated an association between H. pylori infection and mucosa-associated lymphoid tissue lymphoma (MALToma). The most dramatic evidence supporting a pathogenetic role for H. pylori in MALToma is remission of the tumor following eradication of H. pylori with antibiotic therapy. [42]

Key Words: helicobacter Pylori, Idiopathic thrombocytopenic purpura, peptic ulcer, chronic gastritis, gastric B cell lymphoma, hemostasis, autoimmune, hematological pathologies, gastric atrophy, platelets, gastric cancer.

ОШҚОЗОН-ИЧАК САРАТОНИНИ РИВОЖЛАНИШИДА HELICOBACTER PYLORI ИНФЕКТЦИЯСИНИНГ АҲАМИЯТИ

Кириш: Helicobacter Pylori (HP) инфекцияси ошқозоннинг сурункали яллиғланиши ҳамда ошқозон-ичак трактинингсаратон касалликлари ривожланиши билан боғлиқ бўлиши мумкин.

Тадқиқот мақсади: HP инфекциясини ошқозон-ичак трактида саратон касаллигини ривожланишига таъсири билан боғлиқ илмий тадқиқотлар ва адабиётларни кўриб чиқиш.

Материаллар ва усуллар: HP инфекциясини ошқозон-ичак трактида саратон касаллигини ривожланишига таъсири қилувчи механизмларни ўрганиш бўйича илмий адабиётларни ўрганилди.

Натижалар ва уларнинг муҳокамаси: HP - бу ошқозон патогени бўлиб, дунё аҳолисининг тахминан 50 фоизига ўз таъсирини кўрсатади. HP инфекцияси сурункали яллиғланишни келтириб чиқаради ва ўн икки бармоқли ичак ва ошқозон яраси ҳамда ошқозон саратони ривожланиш хавфини сезиларли даражада оширади. HP инфекцияси ошқозон саратони учун энг асосий хавф омили хисобланиб, саратон касаллигидан ўлимга сабаб бўлишда иккинчи ўринда туради. HP ошқозонга муҳитига тушиши билан беморнинг бутун ҳаёти давомида сақланиб қолади, бу эса бактерияни нейтраллашда беморнинг иммун таъсири самарасиз эканлигидан далолат беради. Ушбу шарҳда биз беморнинг иммун таъсирини муҳокама қиламиз ва бактериянинг патоген потенциалини оширадиган бошқа омилларни, шу жумладан бемор полиморфизмларини, апикал-бирикма комплексидаги ўзгаришларни ва атроф-муҳит омилларининг таъсирини ўрганамиз. Шуни ҳам қўшимча қилиш керакки HP штаммларининг таъсири ва реакциялари хилма-хилдир [69].

Хулоса. HPнинг канцерогенезни хосил бўлишдаги аҳамияти тўлиқ ўрганилмаган. Кўплаб тадқиқотлар HP инфекциясини шиллиқ қават (МАЛТ лимфома)билан боғлиқ бўлган лимфа тўқималари лимфомаси ўртасидаги алоқани мавжудлигини кўрсатмоқда. Энг ишончли далилларга биноан HP МАЛТомада патогенетик аҳамияти кўрсатилиб, антибиотик терапияси билан HP эридикация қилинганда ўсманинг ремиссияси кузатилади [42].

Калит сўзлар: helicobacter pylori, идиопатик тромбоцитопеник пурпура, ошқозон яраси, сурункали гастрит, ошқозоннинг Б-ҳужайрали лимфомаси, гемостаз, аутоиммун касалликлар, гематологик патология, ошқозон атрофияси, тромбоцитлар, ошқозон саратони.

РОЛЬ ИНФЕКЦИИ HELICOBACTER PYLORIВ РАЗВИТИИ ЖЕЛУДОЧНО-КИШЕЧНЫХ ЗЛОКАЧЕСТВЕННЫХ НОВООБРАЗОВАНИЙ

Введение: Инфекция Helicobacter Pylori (HP) связана с хроническим воспалением желудка и может также быть связана с развитием желудочно-кишечных злокачественных новообразований.

Цель исследования: в этом исследовании проведен обзор научных исследований и литературы, связанных с инфекцией HP, и её влияние на развитие желудочно-кишечных злокачественных новообразований.

Материалы и методы исследования. Был проведен обзор научной литературы по исследованию инфекции HP и механизм влияния HP-инфекции на развитие желудочно-кишечных злокачественных новообразований.

Результаты и их обсуждения. Helicobacterpylori является желудочным патогеном, который колонизирует приблизительно 50% населения мира. Инфекция H. pylori вызывает хроническое воспаление и значительно увеличивает риск развития язвенной болезни двенадцатиперстной кишки и желудка, а также рака желудка. Инфекция H. pylori является наиболее известным фактором риска развития рака желудка, который является второй по значимости причиной смертности от рака во всем мире. Как только H. pylori колонизирует желудочную среду, она сохраняется в организме в течение всей жизни хозяина, что свидетельствует о том, что иммунный ответ хозяина неэффективен при обезвреживании этой бактерии. В этом обзоре мы обсуждаем иммунный ответ хозяина и исследуем другие факторы хозяина, которые увеличивают патогенный потенциал этой бактерии, включая полиморфизмы хозяина, изменения в апикально-соединительном комплексе и влияние факторов окружающей среды. В дополнение к эффектам и реакциям хозяина, штаммы H. pylori генетически разнообразны [69].

Выводы. Точный механизм объяснения роли H. pylori в канцерогенезе до конца не изучен. Многочисленные исследования продемонстрировали связь между инфекцией H. pylori и лимфомой лимфатической ткани, ассоциированной со слизистой оболочкой (MALTлимфома). Наиболее убедительным доказательством, подтверждающим патогенетическую роль H. pylori в MALToma, является ремиссия опухоли после эрадикации H. pylori с помощью антибиотикотерапии. [42]

Ключевые слова: HelicobacterPylori, идиопатическая тромбоцитопеническая пурпура, язвенная болезнь желудка, хронический гастрит, В-клеточная лимфома желудка, гемостаз, аутоиммунные заболевания, гематологические патологии, атрофия желудка, тромбоциты, рак желудка.

Introduction. Helicobacter pylori (H. pylori) is present in over 50% of all stomachs in the world population, making it the most frequent infection in humans[1]. It displays a marked disparity in occurrence between developed countries, where its prevalence oscillates between 30% and 50%, and developing countries, where its prevalence ranges between 80% and 90%[2].

After 1983, when it was discovered that the stomach could be colonized by bacteria[3], increasing evidence has shown that H. pylori is a pathogen closely related to a variety of gastric conditions. These range from benign stomach diseases such as chronic gastritis, duodenal peptic ulcers and gastric peptic ulcers[3] to malignant diseases such as gastric cancer[4] and gastric mucosa-associated lymphoid tissue (MALT) lymphoma[5].

Helicobacter pylori (H. pylori) is the most common infection in humans, with a marked disparity between developed and developing countries. Although H. pylori infections are asymptomatic in most infected individuals, they are intimately related to malignant gastric conditions such as gastric cancer and gastric mucosa-associated lymphoid tissue (MALT) lymphoma and to benign diseases such as gastritis and duodenal and gastric peptic ulcers. Since it was learned that bacteria could colonize the gastric mucosa, there have been reports in the medical literature of over 50 extragastric manifestations involving a variety medical areas of specialization. These areas include cardiology, dermatology, endocrinology, gynecology and obstetrics, hematology, pneumology, odontology, ophthalmology, otorhinolaryngology and pediatrics, and they encompass conditions with a range of clear evidence between the H. pylori infection and development of the disease. Helicobacter pylori (H. pylori) infections are intimately related to malignant gastric conditions and benign diseases in the stomach [6].

Purpose of Study. Helicobacter pylori is the dominant species of the human gastric microbiome, and colonization causes a persistent inflammatory response. H. pylori-induced gastritis is the strongest singular risk factor for cancers of the stomach; however, only a small proportion of infected individuals develop malignancy. Carcinogenic risk is modified by strain-specific bacterial components, host responses and/or specific host–microbe interactions. Delineation of bacterial and host mediators that augment gastric cancer risk has profound ramifications for both physicians and biomedical researchers as such findings will not only focus on the prevention approaches that target H. pylori-infected human populations at increased risk for stomach cancer but will also provide mechanistic insights into inflammatory carcinomas that develop beyond the gastric niche. [69]

Materials and Methods. A literature review was conducted of reported research of the association of HP infection and gastric cancer cases.

ResultsandDiscussion

KeyPoints

Infection with Helicobacter pylori is the strongest known risk factor for gastric adenocarcinoma, but only a minority of colonized individuals develop cancer of the stomach.

H. pylori strains exhibit extensive genetic diversity and strain-specific proteins augment the risk for malignancy.

β-catenin signaling has an important role in conjunction with other oncogenic pathways in the regulation of host responses to H. pylori that have carcinogenic potential.

Transactivation of epidermal growth factor receptor may help us understand the epithelial signaling pathways that mediate H. pylori-induced carcinogenesis.

Chronic inflammation can induce aberrant β-catenin activation in the context of H. pylori infection.

A mechanistic understanding of H. pylori activation of oncogenic signaling may lead to key insights into malignancies that arise from inflammatory foci in other organ systems [7].

Gastric adenocarcinoma is the second leading cause of cancer-related death in the world [1]. Epidemiological and interventional studies in humans, as well as experiments in rodents, have associated Helicobacter pylori — a member of a large family of related bacteria that colonize the mammalian stomach — with peptic ulcers, non-Hodgkin's lymphoma of the stomach, gastric atrophy and distal gastric adenocarcinoma [10-18]. However, only a small percentage (probably less than 3%) of individuals that carry H. pylori ever develop neoplasias related to its presence, indicating that other factors are involved. Such observations, along with recent evidence that certain H. pylori strains might reduce the risk of GASTROESOPHAGEAL REFLUX DISEASE (GERD) and its complications (for example, oesophageal adenocarcinoma) [19, 20], underscore the importance of understanding the biological interactions of these organisms with their host [9].

H. pylori and gastric cancer

Two histologically distinct variants of gastric adenocarcinoma have been described, each having different epidemiological and pathophysiological features. Intestinal-type gastric adenocarcinoma usually occurs at a late age, predominates in men and progresses through a relatively well-defined series of histological steps [8]. Diffuse-type gastric adenocarcinoma more commonly affects younger people, affects men and women equally and consists of individually infiltrating neoplastic cells that do not form glandular structures and are not associated with intestinal metaplasia[21].

The chain of events that occurs during development of intestinal-type gastric cancer involves a transition from normal mucosa to chronic superficial GASTRITIS, which then leads to ATROPHIC GASTRITIS and INTESTINAL METAPLASIA, and finally to DYSPLASIA and ADENOCARCINOMA. The ability of H. pylori to induce superficial gastritis [22], however, indicates that this organism — or the host inflammatory response to it — could be important in the initiation and promotion of gastric neoplasia. [9].

Histologically, two distinct variants of gastric carcinoma have been identified: diffuse-type gastric cancer, which consists of individually infiltrating neoplastic cells that do not form glandular structures; and intestinal-type adenocarcinoma, which progresses through a series of well-defined histological steps and was first described in 1975 [22, 23] (Fig. 1). Intestinal-type adenocarcinoma is initiated by the transition from normal mucosa to chronic superficial gastritis; this is followed by atrophic gastritis and intestinal metaplasia, finally leading to dysplasia and adenocarcinoma [22, 24, 25]. This form of gastric cancer affects men twice as commonly as women and occurs in men with a mean age of 50.4 years and in women with a mean age of 47.7 years.Corpus-predominant gastritis predisposes individuals toward gastric cancer, which is thought to be due in part to decreased acid secretion. In contrast, infection primarily of the gastric antrum results in increased acid production and predisposes individuals to duodenal ulcer disease, which is associated with a decreased risk of gastric cancer [22].

Multifactorial pathway leading to gastric carcinoma. Many host, bacterial, and environmental factors act in combination to contribute to the precancerous cascade leading to development of gastric cancer.

H. pylori can cause chronic active gastritis and atrophic gastritis, early steps in the carcinogenesis sequence [26, 27]. In animal models, H. pylori infection has induced gastric adenocarcinoma [28]. Furthermore, a number of studies in humans have demonstrated a clear association between H. pylori infection and gastric adenocarcinoma [29-31]. The link has been demonstrated in both the intestinal and diffuse subtypes of gastric cancer [29,32].

The relationship between H. pylori infection and gastric carcinogenesis in humans can be illustrated by the following observations:

●H. pylori has been identified histologically in the uninvolved mucosa from stomachs harboring cancers or precancerous changes e.g. atrophic gastritis with or without accompanying intestinal metaplasia [33,34].

●Epidemiologic studies demonstrate a strong correlation between H. pylori seropositivity and gastric cancer. As an example, the EUROGAST study of 17 populations from 13 different countries (11 European countries, the United States, and Japan) found a six fold increased risk of gastric cancer in H. pylori-infected populations compared with uninfected populations [35]. Similar findings have been noted in nested-case control studies in which the stored serum of patients with known gastric adenocarcinoma and that of matched controls were tested for H. pylori IgG antibody. H. pylori infection was associated with odds ratios ranging from 2.8 to 49 and attributable risks of 46 to 63 percent [31,36-39]. In a nested case control study of Japanese Americans living in Hawaii, for example, H. pylori seropositivity was present in 94 percent of patients with gastric cancer compared with 76 percent of matched controls; the odds ratio was 6.0 [37].

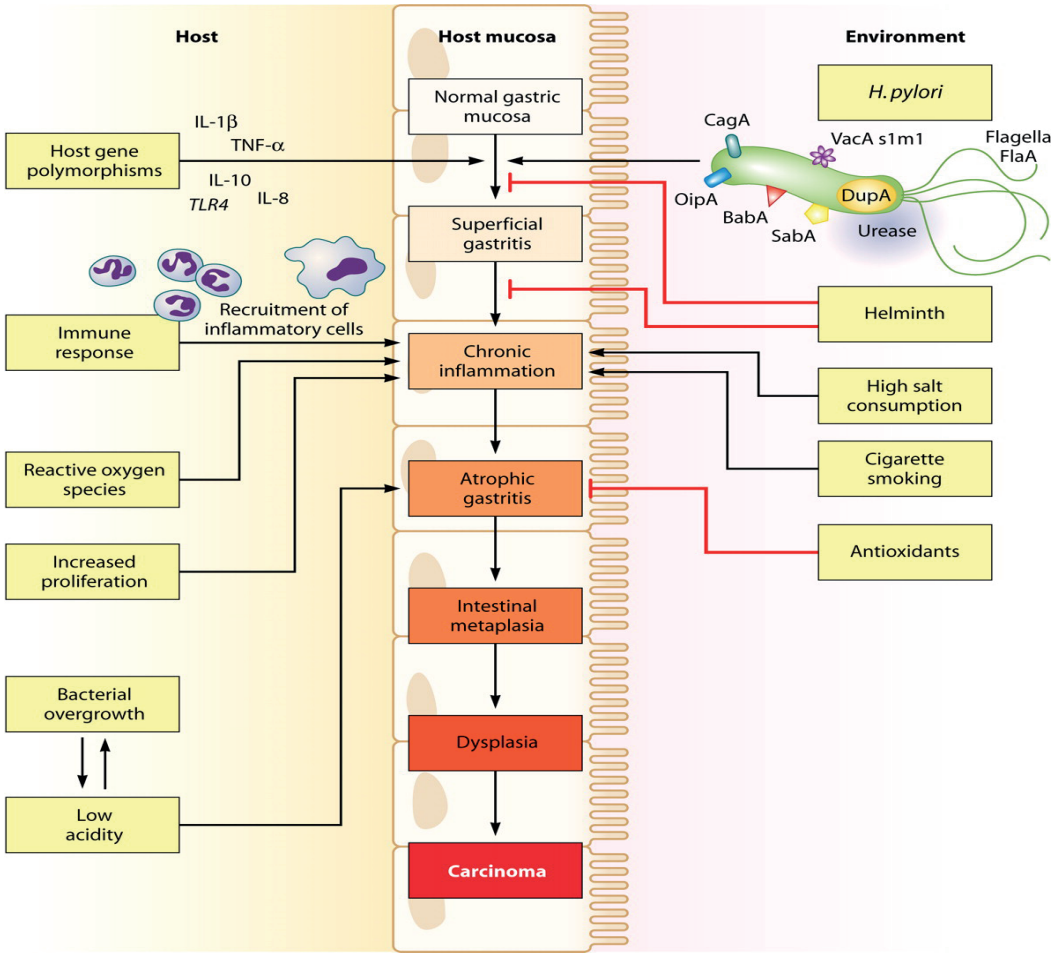

FIG. 1.

●Two meta-analyses of cohort and case control studies examining the relationship between H. pylori seropositivity and gastric cancer found that H. pylori infection was associated with a twofold increased risk for developing gastric adenocarcinoma [29,30]. The relative risk for gastric cancer was greatest for younger patients (9.29 at age less than 29) in whom the absolute risk is still quite low [29].

One of the largest prospective studies addressing H. pylori and cancer risk included 1,526 Japanese patients of whom 1,246 had H. pylori infection [40]. Patients underwent endoscopy with biopsy at enrollment and then between one and three years after enrollment. During a mean follow-up of 7.8 years, 36 patients developed gastric cancer (2.9 percent), all of whom were H. pylori infected. No uninfected patient developed cancer.

The International Agency for Research on Cancer estimates that 36 and 47 percent of all gastric cancers in developed and developing countries, respectively, are solely attributable to H. pylori infection. This accounts for almost 350,000 gastric cancers annually worldwide. One report indicated that of the 12.7 million new cancers occurring in 2008, the population attributable fraction due to infections was over 16 percent for H. pylori [41,42].

Despite the clear association between H. pylori and gastric adenocarcinomas, only a minority of infected individuals will develop gastric cancer. It is thought that modulation of the effects of infection by external, mostly environmental factors (and possibly strain differences in H. pylori, see below) influence whether infection results in a neoplastic or non-neoplastic process.[42]

Role of H. pylori in carcinogenesis — Several hypotheses have been proposed to explain the role of H. pylori in carcinogenesis, although the exact mechanism is incompletely understood [42,43]. At present, it is believed that bacterial properties, host response, and environmental factors all play a role.

H. pylori strain differences — The strain of H. pylori also may be a determinant of its potential to cause cancer or ulcer disease.

Host immune responses — Host genetics that regulate the immune response and mucosal events that result from infection play important roles in gastric cancer development in chronically infected individuals [42].

Cytokine polymorphisms — Certain polymorphisms in IL-1 beta and other cytokines may confer an increased susceptibility to non-cardia gastric adenocarcinoma caused by H. pylori by inducing a hypochlorhydric and atrophic response to H. pylori infection [42,44-49]. An illustrative study compared IL-1 beta polymorphisms in 393 patients with gastric cancer with 430 controls [42,44]. Two specific polymorphisms (IL-1B-31T and IL-1RN*2) were associated with low acid secretion and gastric atrophy. The authors concluded that 38 percent of H. pylori-related gastric cancer could be attributed to the presence of these alleles. IL-1 beta, a potent inhibitor of gastric acid secretion, is upregulated by the presence of H. pylori [42].

A similar report compared polymorphisms in genes for several cytokines in patients with a variety of gastric and esophageal malignancies with a control population [42,45]. Proinflammatory genotypes of tumor necrosis factor alpha and IL-10 were associated with more than a doubling of the risk of non-cardia gastric cancer. Carriage of multiple proinflammatory polymorphisms of IL-1 beta, IL-1 receptor antagonist, tumor necrosis factor A, and IL-10 conferred even greater risk (OR 2.8 for one, 5.4 for two, and 27.3 for more than three). By contrast, these polymorphisms were not associated with an increased risk of esophageal or gastric cardia cancers.[42]

These data suggest that gene polymorphisms influence cytokine expression, gastric inflammation, and risk for development of precancerous lesions in those infected with H. pylori. Infection with certain virulent bacterial strain types augments inflammation and cancer risk, supporting a complex interaction between host and bacterial in the development of GI pathology [50].

Neutrophil activation — One hypothesis has been demonstrated in vitro. CD11a/CD18- and CD11b/CD18-neutrophils, induced by H. pylori infection, interact with intercellular adhesion molecule-1 (ICAM-1), resulting in the migration of neutrophils to the site of infection and adhesion to the surface epithelium. The recruited neutrophils then produce inducible nitric oxide synthase and release nitric oxide and reactive oxygen metabolites, such as superoxide and hydroxyl ions, which in turn damage DNA. This is followed by mutation and malignant transformation. H. pylori induces oxidative stress in epithelial cells [51].

Epithelial responses — H. pylori and the immune response induce altered rates of gastric epithelial cell growth and death, which involve various signaling pathways leading to apoptosis, proliferation, differentiation, and autophagy [42].

Apoptotic pathways — Two important processes in carcinogenesis are apoptosis (programmed cell death) and hyperproliferation [52]. Following severe DNA damage, apoptosis occurs as a protective mechanism to prevent replication of mutated DNA. Atrophic gastritis with destruction and loss of the glands could be the result of apoptosis. This hypothesis is supported by the finding of an increased rate of antral apoptosis in H. pylori-infected subjects [42,53,54], which returns to normal following eradication therapy [53]. The mechanism by which H. pylori induces apoptosis is unclear. One study suggested that the organism causes apoptosis by both direct and indirect mechanisms [55]. In the latter circumstance, H. pylori appears to sensitize epithelial cells for apoptosis which is induced by proinflammatory stimuli (e.g. tumor necrosis factor alpha). H. pylori enhances expression of the Fas receptor on gastric epithelial cells and may mediate apoptosis through signaling mechanisms related to the Fas death receptor [56]. Proliferating cells may be resistant to apoptosis. This would upset the balance between cell growth and death, leading to hyperproliferation and the promotion of neoplasia [57]. There is evidence of an increased amount of the anti-apoptosis protein, Bcl-2, in the setting of gastric dysplasia [58]. Other reports have found that apoptosis may be due to plasminogen activator inhibitor (PAI)-2, the expression of which is increased by H. pylori. PAI-2 is increased in gastric cancer [59]. An uncoupling of epithelial proliferation and apoptosis may be a strain-dependent phenomenon. Hyperproliferation has been seen in CagA-infected patients in whom apoptosis is not increased [60].

Cell signaling events — One report indicated that c-Src and c-Abl kinases sequentially phosphorylate CagA [61]. The two phosphorylation events need not occur on the same CagA molecule but are both required for the biological effects of CagA. Another study demonstrated that vacuolating cytotoxin and variants in Atg16L1 disrupt autophagy and promote H. pylori infection in humans. As autophagy protects against infection with H. pylori, this could contribute to inflammation and eventual carcinogenesis [62]. A potentially important observation is that the source of gastric cancer may not be from gastric epithelial cells themselves but rather from bone marrow-derived cells that differentiate into gastric epithelial cells in the presence of H. pylori [63]. If this observation is confirmed, it would have significant implications for the treatment of H. pylori-associated gastric cancer as well as other epithelial cancers associated with chronic

inflammation [42].

Colon cancer—An association between H. pylori infection and colorectal polyps and colorectal cancer has been described but remains controversial [70-81].

The biologic basis for such an association is uncertain. One possibility is elevated serum gastrin levels in patients with H. pylori infection [71]. Gastrin receptors have been identified on a variety of colon cancer cell lines, and endogenous serum gastrin levels have been correlated with the risk of colonic neoplasms. However, studies have not found an association of serum gastrin levels with an increased risk for colonic neoplasia [77,80].

Pancreatic cancer—An association between H. pylori infection and pancreatic cancer has been reported [82-86]. In a meta-analysis that included 1083 patents with pancreatic cancer and 1950 controls, infection with H. pylori was associated with an increased risk of pancreatic cancer (OR 1.47, 95% CI 1.2-1.8) [87]. On subgroup analysis, CagA positive H. pylori strains were not associated with an increased risk of pancreatic cancer. Another report found an association between colonization with non-CagA H. pylori strains and pancreatic cancer in patients with non-O blood types; no association was found in patients with non-O blood types infected with CagA positive H. pylori [84].

A possible mechanism proposed for the association of pancreatic cancer and H. pylori is the link between pancreatic cancer and chronic hyperacidity [88]. Additional studies are needed to confirm the association of pancreatic cancer and H. pylori infection and also to better support the putative role of hyperacidity.

Hepatobiliary cancer—Several studies report an association between biliary tract carcinoma and infection with H. pylori [89-93]. Although a cause and effect relationship has not been proven, some have suggested that H. pylori may be involved in the pathogenesis of biliary neoplasms through enhanced biliary cell inflammation and proliferation [92, 94].

Does treatment reduce risk of gastric cancer?

Eradication of H. pylori appears to reduce the risk of gastric cancer. The magnitude of reduction varies by the baseline incidence of gastric cancer, but is seen even in populations with low gastric cancer incidence. A meta-analysis of 27 studies included 48,606 H. pylori infected individuals with 715 incident gastric cancers [64]. Individuals with eradication of H. pylori had a lower incidence of gastric cancer as compared with those who did not receive eradication therapy (pooled incidence rate ratio 0.53; 95% CI 0.44-0.64). As compared with individuals in the lowest tertile of baseline cancer incidence, those in the intermediate and highest tertile of cancer incidence had a greater reduction in gastric cancer incidence rate with H. pylori eradication (incidence rate ratio 44 and 38 percent, respectively). The magnitude of benefit was not significantly different between asymptomatic individuals and those who had undergone endoscopic resection of gastric cancer [42].

Even if treatment does reduce the gastric cancer risk, difficulties with screening for H. pylori and treatment arise. The cost of screening and treating would be large given the worldwide prevalence of H. pylori infection. Nevertheless, one study that economically modeled the cost of screening per year of life saved estimated that, in selected populations such as Japanese American, serologic screening for H. pylori beginning at age 50 was more beneficial than breast cancer screening [65]. Another cost-effectiveness analysis concluded that screening and treatment could be cost-effective if the cancer risk following eradication could be restored to that of a population that had never been infected with H. pylori [67].

A number of major medical organizations have issued guidelines related to H. pylori screening and eradication in high-risk populations. As examples, Asian-Pacific guidelines and European guidelines support population-based screening in high-risk settings [67,68].

Approximately 36 and 47 percent of all gastric cancers in developed and developing countries, respectively, are solely attributable to H. pylori infection. This accounts for almost 350,000 gastric cancers annually worldwide.

Conclusion. Several hypotheses have been proposed to explain the role of H. pylori in carcinogenesis, although the exact mechanism is incompletely understood. (See ‘Role of H. pylori in carcinogenesis’ above.) Multiple studies have demonstrated an association between H. pylori infection and mucosa-associated lymphoid tissue lymphoma (MALToma). The most dramatic evidence supporting a pathogenetic role for H. pylori in MALToma is remission of the tumor following eradication of H. pylori with antibiotic therapy [42].

Conflict of interest statement. Competing interests: the authors of this paper have no conflict of interest to disclose.

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