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Changing the natural history of metachronous gastric cancer after *H. pylori* eradication

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Abstract

Metachronous gastric cancer occurs frequently following endoscopic removal of an early gastric cancer. *H. pylori* eradication significantly reduces that risk. While, the pathogenesis of this phenomenon remains unclear, it is clear that the natural history of metachronous gastric cancer is altered following *H. pylori* eradication. Genetic instability of host cells induced by inflammation, *H. pylori*, host or environmental factors can result in the production of malignant cells. *H. pylori* eradication reduces and alters the inflammation, and can reverse epigenetic damage and abnormal expression of miRNA's. Fundamentally, *H. pylori* eradication stops the progression and may reverse some of the damage to the mucosa resulting in improved acid secretion and improving the gastric microbiome. Because the risk of developing metachronous cancer varies among patients, prospective research is needed to identify reliable biomarkers to predict development of metachronous cancer as well as to define surveillance methods, intervals, and duration. Some candidate examples of prognostic or predictive biomarkers for the prediction of subsequent risk include the presence or absence, titers, and changes in anti-*H. pylori* IgG and or anti-CagA antibodies, serum pepsinogens, gastrin, and miRNAs.

Introduction

Helicobacter pylori (*H. pylori*) infection is a class I human carcinogen and a necessary but insufficient causative factor in gastric cancer. The pathogenesis of the gastric cancer is multifactorial with cancer being an end product of the decades-long interaction between the organisms and the host. The major drivers of *H. pylori*-related gastric carcinogenesis are chronic inflammation along with *H. pylori*-mediated genetic and epigenetic changes resulting in genetic instability in host cells[1,2]. Environmental factors are important as changes in diet and food preservation can enhance or reduce the severity of *H. pylori*-induced gastric mucosal damage and result in a change in the primary outcome of the infection[3, 4]. The local environment in the stomach is also important in that *H. pylori* inflammation and mucosal damage can result in hypochlorhydria/achlorhydria which allows intragastric growth of non-*H. pylori* bacteria that promote biotransformation of ingested or secreted compounds (eg, nitrates) to produce carcinogens[5-7].

H. pylori infection promotes field cancerization. Field cancerization was described by Slaughter et al. in the early 1950's to explain the presence of multicentric cancers occurring in oral stratified squamous epithelium[8]. The concept is based on the fact that carcinogens act widely within a mucosal field thus resulting in multi-centric disease. In 1961 at the 4th National Cancer Conference Proceedings, Leslie Foulds summary of field cancerization provides an excellent introduction to gastric cancer. He wrote, “The carcinogen establishes a state of incipient neoplasia coextensive with the area of exposure to a carcinogen. At this stage, corresponding with initiation, there is not necessarily any multiplication of cells or other specific clinical or histologic abnormality, yet the tissue is permanently altered and has acquired new capacities for progression to overt neoplasia. After considerable delay, with or without further extrinsic stimulation, visible lesions emerge focally or multifocally within the region. Malignant tumors emerge still later; some develop by progression in the lesions established in the preceding stage, but some *emerge* at places where no precursor lesion has been seen; they may emerge consecutively for long periods after those lesions have regressed. The early lesions are subject to diverse fates; some regress, some persist indolently, some grow progressively as benign tumors and some, usually a small minority, undergo progression to malignant neoplasia. They are “precancerous” only in the sense of having a certain statistical probability of progression to carcinoma. Carcinoma in situ is interpreted as an imperfect carcinoma whence invasive carcinoma may develop by a progression that confers the property of invasiveness which was not present in the earlier lesion.[9] as reported by Bockus[10] page 748. This succinct description provides an excellent overview of progressive nature of *H. pylori*-induced gastric mucosal damage resulting in cancer and provides a basis for understanding why metachronous tumors often appear after removal of an initial early gastric cancer.

H. pylori causes progressive gastric mucosal damage

The association of atrophic gastritis and gastric cancer has been a focus of research since the late 19th century[11]. Initially *H. pylori* infection and mucosal damage is most severe in the antrum and later progresses proximally into the gastric corpus as an advancing band of inflammation that results in an ever enlarging “lawn” of metaplastic pyloric type epithelium. This epithelium was originally termed pseudopyloric metaplasia by Stoerk to describe the mucosa that repopulated the stomach following diphtheria-induced acute gastritis (as related by Faber). When stained with hematoxylin and eosin pseudopyloric mucosa is easily confused with antral mucosa and unless the pathologist is informed that the biopsy was definitely from corpus mucosa, it is not likely to be recognized as a metaplastic epithelium. Until recently, the primary method of identifying pseudopyloric metaplasia in gastric biopsy specimens was to stain for the presence of pepsinogen I secreting cells which are normally restricted to the corpus[13]. Pseudopyloric metaplasia is now easily recognized because it stains positive for spasmolytic polypeptide and after decades of being ignored it is now a focus of research as spasmolytic polypeptide expressing epithelium[14-16]. This metaplastic epithelium is thought to arise by transdifferentiation of chief cells[16, 17] and it has been suggested that both intestinal metaplasia and gastric cancer may arise from spasmolytic polypeptide expressing epithelium[16-18]. However, many no longer consider intestinal metaplasia a definite precursor of gastric cancer but rather as an easily recognized

manifestation of atrophic gastritis[19, 20] {Hattori, 1986 17952 /id.} It remains unclear whether the transdifferentiation is reversible; this will be discussed briefly below.

Pathogenesis of gastric mucosal damage and genetic instability

As noted above, the pathogenesis of gastric cancer depends on the presence of mutated gastric cells (eg, genetic instability) coupled with their acquisition of the ability to evade immune destruction, suppress the immune response and persist. Genetic instability of the gastric mucosa arises from three principle mechanisms: as a consequence of *H. pylori*-induced acute and chronic inflammation, because of direct bacterial host interactions, and because of interactions with exogenous factors to produce carcinogens locally in the stomach[1]. Gastric cancer is an inflammation-associated cancer that occurs as a result of the infection which causes chronic, often life-long, gastric mucosal inflammation histologically characterized as acute-on-chronic inflammation (Figure 1)[1, 2].

As noted above, *H. pylori* is a necessary but insufficient cause of gastric cancer which is typical of infectious causes of cancer such as human papilloma virus and cervical cancer or hepatitis C infection and liver cancer in that a malignancy only occurs in a subset of patients and the risk is often enhanced by the presence of environmental factors that enhance carcinogenesis. Bacterial, host, environmental interactions are responsible for the marked geographic differences in gastric cancer incidence as well as for the rapid changes in gastric cancer incidence that have been noted in association with changes in diet and food preservation in the West and more recently in Asia[3, 4]. A high incidence of gastric cancer in a population is associated with environment factors conducive to the early development of atrophic gastritis and hypo/achlorhydria. Risk is further enhanced by the presence of a more virulent strain of *H. pylori*[21]. A number of putative virulence factors such as the cag pathogenicity island (eg, CagA positive strain) have been identified as associated with an increased risk of a clinical outcome such as peptic ulcer or gastric cancer. While none of the virulence factors has disease specificity, they typically are associated with an increased host inflammatory response[21]. Importantly, no avirulent strain has been described; all *H. pylori* cause gastric inflammation and can result in gastric cancer. The difference in cancer risk between the most and the least virulent is probably less than 3-fold and leading to the recommendation that all *H. pylori* infections be eradicated[21].

H. pylori infection also stimulates immune lymphocytes in the gastric mucosa and immune cells constituting mucosa-associated lymphoid tissue (MALT) which migrate to and infiltrate the sites of *H. pylori* infection in the stomach[22] where chronically produced inflammatory cytokines may contribute to tumor promotion and progression[23]. In an inflammatory state, cell turnover is high rate and the micro-environment is often highly oxidative and nitrosative which results in increasing the opportunities for DNA damage and somatic mutation[2, 24].

H. pylori-induced gastric cancer

Genetic instability, whether induced by inflammation, *H. pylori*, host or environmental factors can result in the production of malignant cells. The host is normally protected by

innate and adaptive immune responses from the attack of pathogens. In the inflammatory microenvironment produced by the infection, there is a balance between antitumor immunity and tumor-originated pro-inflammatory activity[25]. These cells interact with the immune system which attempt to destroy them as “non-self”[26]. If potential malignant cells survive, they may remain as a small focus held in check by the immune system and require additional genetic (immuno-editing) changes to escape the immune system and become visible as an intramucosal neoplasia. Accumulation of additional mutations can result in acquisition of invasiveness which allows an early gastric cancer to metastasize and become the cause of the host's demise.

H. pylori itself can directly cause genetic instability (Figure 2). For example, *H. pylori* infection can induce methylation of multiple CpG islands including methylation of E-cadherin which is a tumor suppressor gene[27]. This hypermethylation is potentially reversible following *H. pylori* eradication[28-30]. *H. pylori* also stimulates activation-induced cytidine deaminase (AID) which induces nucleotide alterations involved in DNA mutations[31]/ Aberrant AID expression is widely detectable not only in cancer lesions but also in *H. pylori* chronic gastritis[32, 33]. *H. pylori* infection has also been shown to lead to double-stranded DNA breaks in host DNA as well as to disordered regulation of microRNA production, all of which may increase genetic instability and be related to the increased risk of gastric cancer[1, 2]. Importantly all these events are present in all *H. pylori* infected individuals emphasizing the potentially critical role of host and environmental interactions in possibly affecting repair mechanisms resulting in differences in the rate of accumulation of genetic damage.

Effect of *H. pylori* eradication on gastric cancer risk

H. pylori eradication stops the progression and may reverse some of the damage to the mucosa. The risk of developing gastric cancer is related to the development and extent of atrophic gastritis such that cure of the infection while non-atrophic mucosa stops the process and cancer risk remains minimal to absent. Thus, the benefit obtained by eradication is proportional to the baseline cancer risk at the time *H. pylori* eradication occurs. The natural history of *H. pylori* gastritis is progression of damage which results in an exponential increase in risk. *H. pylori* eradication is expected to stop the progression and to stabilize or reduce the risk. In addition, if parietal cells remain, but are suppressed by inflammatory mediators (eg, IL-1 β), improved acid secretion occurs would further reduce or eliminate any untoward effects associated with overgrowth with non-*H. pylori* bacteria[34]. These expectations can be seen in recent large studies. For example, a large-scale cohort study from Taiwan followed 80,000 patients with peptic ulcer for 10 years after *H. pylori* eradication therapy[35]. The patients were assigned to an early eradication group (patients underwent *H. pylori* eradication therapy at the time of diagnosis) or a late eradication group (patients underwent *H. pylori* eradication therapy 1 year after diagnosis). The incidence of gastric cancer was markedly lower in the early eradication group than in the late eradication group suggesting that, while the effect of *H. pylori* eradication therapy in reducing the incidence of gastric cancer is obvious, the earlier eradication the better.

Mass eradication of *H. pylori* was started in Taiwan in 2004 and initially included 4,121 subjects. Compared to the 5 year period before *H. pylori* therapy, the effectiveness of *H. pylori* eradication therapy in reducing the incidence of gastric cancer was estimated to be 25% (rate ratio 0.753, 95% CI 0.372 to 1.525)[36]. Identification of a significant effect of eradication on cancer prevention will often depend on the duration of follow-up duration (i.e., whether the duration is sufficiently long to allow the difference to become evident)[37]. This is shown in the Shangdong intervention trial which failed to find a difference in gastric cancer incidence after 7.3 years but after 14.7 years the incidence of gastric cancer was significantly reduced among those who had received *H. pylori* eradication therapy[38].

Metachronous gastric cancer

The phenotype of the individual at risk for gastric cancer includes the presence of extensive atrophic gastritis. The entire gastric mucosa is exposed to *H. pylori* and intraluminal carcinogens (i.e., field carcinogenesis) and thus it is not surprising that gastric cancer is often multifocal. For example, careful examination of stomachs resected for one cancer report that 4% to 15% will contain an identifiable foci of cancer separate from the lesion which prompted the resection[39-41]. It is thus unclear how many metachronous lesions are new lesions vs. appearance of missed or previously inapparent synchronous lesions.

The surprising finding following *H. pylori* eradiation after removal of an early gastric cancer was that *H. pylori* eradication reduced the rate of metachronous lesions approximately 3-fold. This was originally reported by Uemura et al. in a prospective nonrandomized study and confirmed by Fukase et al. in a multicenter randomized trial[42, 43]. Since that time there have been a relatively large number of studies and a meta-analysis confirming that *H. pylori* eradication is associated with a reduction in the incidence of metachronous gastric cancer[44]. While the pathogenesis of this phenomenon remains unclear, it is clear that the natural history of the disease is altered following *H. pylori* eradication. *H. pylori* eradication alters or greatly reduces the direct *H. pylori*-associated *H. pylori*-induced inflammation (Figure 1). In addition, there are likely significant changes the interactions of the host's immune system and residual premalignant and as yet inapparent areas of tumorigenesis. For example, regression of acute inflammatory cells and cytokines may also reduce immune mediated tumor-promoting activity[45, 46]. Removal of the *H. pylori* also reduces or eliminates ongoing *H. pylori*-induced direct and epigenetic genetic damage and abnormal expression of miRNA's[47]. Finally, improvement in acid secretion would also be expected to reduce *non-H. pylori* bacterial overgrowth and its potentially deleterious effects[1].

Risk of development of a metachronous gastric cancer

Little is known regarding the relation of a metachronous lesion and its relation to the original early gastric cancer in terms of similarities in genetic signatures, expression of tumor-specific antigens, or natural history. Table 1 lists risk factors that have been suggested as indicative of an increased risk of developing a metachronous lesion. The majority of these have been identified in retrospective analyses and not yet by prospective trials. Most are also the same risk factors that are associated with development of the original cancer such as extent and severity of atrophy and age. Prospective research is needed to identify reliable

biomarkers predictive of development of metachronous cancer as well as to define surveillance methods, intervals, and duration.

Prospective studies also must stratify patients in relation to suspected risk factors in that the incidence of metachronous cancers is low (typically less than 5% per year) making randomization critical to reduce bias. Some candidate examples of prognostic or predictive biomarkers for the prediction of subsequent risk include the presence or absence, titers, and changes in anti-*H. pylori* IgG and or anti-CagA antibodies, serum pepsinogens, gastrin, and miRNA's. The location, extent, and severity of histologic changes before and after *H. pylori* eradication, the effect on acid secretion and gastric microbiome may also be candidate biomarkers.

CD44 (CD44v9) has been identified as one of the cell surface markers associated with cancer stem-like cells[48)] (CD44v9) and is associated with suppression of the production of reactive oxygen species resulting in subsequent therapeutic resistance, recurrence, and metastasis of tumors[48-51)]. A recent report demonstrated that the recurrence rate of early gastric cancer was significantly higher in the CD44v9-positive group than in the CD44v9-negative group (hazard ratio (HR), 21.8; 95% confidence interval (CI), 5.71–83.1).[52)] suggesting the presence of CD44v9 as a possible marker of more rapid recurrence and a poor outcome.

Possible approaches to reducing risk

Clinical trials might include randomized trials of whether the use of adjuvants in addition to *H. pylori* eradication can further reduce risk (i.e., co-therapy with anti-inflammatory agents, gastroprotectives, antioxidants, or demethylating agents)[53-55)]. The gastric microbiome both luminal as well as mucosal is likely to be greatly influenced by *H. pylori* eradication therapy and deserves detailed study. As noted above, the stomach of a patient with an endoscopically removable early gastric cancer likely contains other lesions. Decades ago the congo red-methylene blue test was proposed to assist in identifying such lesions[56)]. Since that time there have been tremendous improvements in imaging technology and these advances should be explored for their utility.

If patients at increased risk could be reliably identified they would seem to be ideal candidates for targeted therapy or for cancer immunotherapy to eliminate residual disease before it becomes evident. It is becoming possible to culture gastric cells as “organoids” such it may be possible to culture the early gastric cancer initially removed to provide the antigens needed for patient-specific vaccination or other immunotherapy[57, 58)]. In addition, targeted chemotherapy based on markers is beginning to show promise and may be useful for patients at especially high risk. For example, Sox2 is a member of the SRY-related HMG-box (SOX) family of transcription factors and well known as an essential embryonic stem cell gene. SOX2 is aberrantly expressed in many solid tumors and is a potential immunogenic antigen. SOX2 actives AKT signaling and has shown neoplastic transformation effect in gastric cancer cell lines and has been identified as an oncogene in gastric cancer[59)]. Cells overexpressing SOX2 also showed significant insensitivity to therapeutic antibody against human epidermal growth factor receptor 2 (HER2)[59)]. HER2

belongs to a family of four receptors (EGFR/HER1, HER2, HER3, HER4). HER regulate cell growth, survival and differentiation through interlinked signal transduction involving activation of the PI3K/ Akt and the Ras/Raf/MEK/MAPK pathways[60]. The monoclonal antibody against HER2 (trastuzumab) is approved as adjuvant treatment specifically for patients with HER2-positive early stage breast cancer and trastuzumab plus chemotherapy showed a survival benefit for advanced gastric cancer patients[61, 62]. Risk stratification may allow appropriate early use of targeted therapy.

Reversal of gastric mucosal atrophy

There are data in humans regarding the use of steroid therapy to promote recovery of normal mucosal histology in atrophy gastritis/gastric atrophy[63-67]. Such studies were typically done long before *H. pylori* was recognized and included both autoimmune and *H. pylori* gastritis. More recently, patients and animals taking tamoxifen have been shown to have regression in intestinal metaplasia, ADP ribosylation inhibitors such as Olaparib™ and prostaglandin E2 have been shown in animal studies to partial reverse intestinal metaplasia suggesting that it may be possible to at least partially reverse these changes[68-72]. More studies are needed especially those coupled with estimates of the changes in cancer risk as well as whether genetic instability has been improved. Possibly these changes are largely cosmetic and relate to changes in transdifferention and thus have little effect with regards to modifying underlying cancer risk[73].

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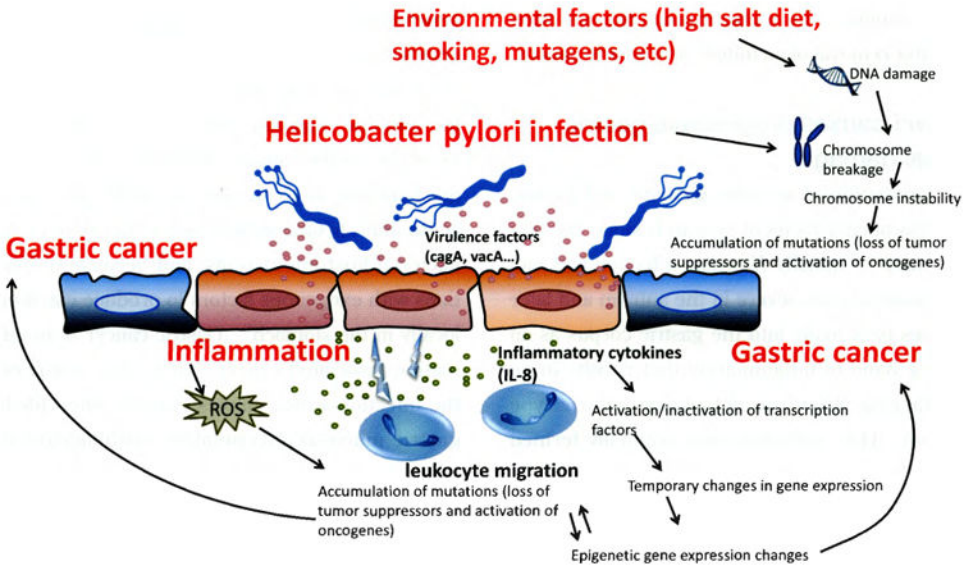

Figure 1. Inflammation-host-bacterial interactions leading to gastric cancer (Adapted from reference[1], with permission)

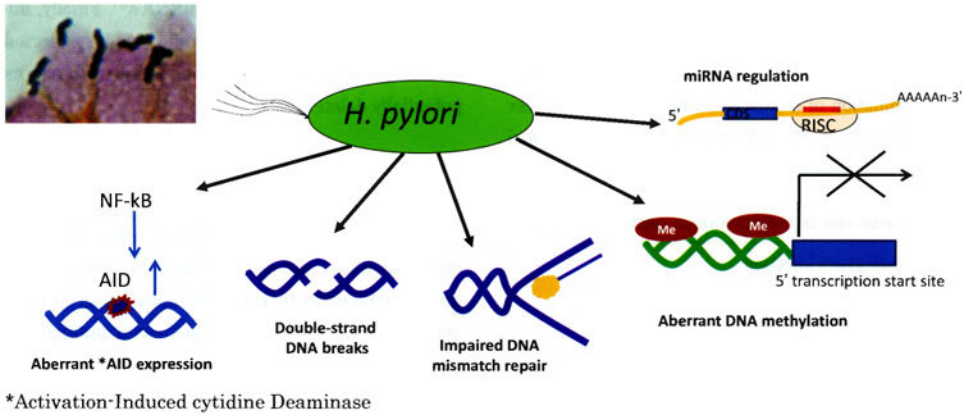

Figure 2.

H. pylori host-cell interactions causing genetic instability (Adapted from reference [1], with permission)

Table 1

Risk factors suggested to be indicative of an increased risk of metachronous gastric cancer.

• Active *H. pylori* infection
• Increased age
• Severity of atrophic gastritis
• Aberrant DNA methylation
• Microsatellite instability
• Aberrant expression of miRNAs
• CD44vO expression by the tumor cells
• Microscopic foci of intramucosal neoplasia elsewhere in the stomach