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Helicobacter Pylori Infection: Independent Risk Indicator of Gastric Adenocarcinoma and The Role of Surgery

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ABSTRACT

Background: Helicobacter pylori is a ubiquitous organism that is current in about half of the global population. Chronic infection with helicobacter pylori causes atrophic and even metaplastic changes in the stomach, and it has a known association with peptic ulcer disease. This bacterial species colonizes the stomach of the greater part of the total populace; notwithstanding, only a very small proportion of infected subjects improve adenocarcinoma. helicobacter pylori causes a chronic gastritis that might last periods, and a multistep precancerous process is documented for the most common histologic type of gastric adenocarcinoma: the intestinal type.

Objectives: Distinguishing of individuals at high risk for gastric cancer.

Conclusion: This article briefly summarizes the main aspects concerning gastric adenocarcinomas and the carcinogenic effects of HELICOBACTER pylori infection.

Keywords: Gastric Cancer, Gastric Adenocarcinoma, Helicobacter Pylori, Multifocal Atrophic Gastritis, Dysplasia.

INTRODUCTION

Helicobacter pylori is a ubiquitous organism that is current in about half of the global population. Chronic infection with helicobacter pylori causes atrophic and even metaplastic changes in the stomach, and it has a known association with peptic ulcer disease. The most common route of helicobacter pylori infection is either oral-to-oral or fecal-to-oral contact [1]. Even though gastric cancer frequency and mortality rates have been slowly reducing in many countries over the last decades, gastric cancer is still the second most common cause of cancer-related deaths and the fourth most common malignancy worldwide. Approximately one million cases were estimated for 2008, 70% of them in less developed areas [2] (Table 1).

Generally, gastric cancer has a poor prognosis. In the US, 66% of the cases are diagnosed when the tumor has extended some degree of dispersal through the gastric wall, and the general five-year survival rate is 25% [3]. For most of the twentieth century the search for the causes of cancer highlighted the role of ionizing radiation and exposure to chemical carcinogens, particularly tobacco smoke, which is a familiar risk factor for malignancy in multiple organs, comprising the stomach [4]. The twenty-first century has carried more care to infectious agents and chronic active inflammation as primary causes of some cancers. Considerable indication has become obtainable for the oncogenic role of two virus families: papilloma viruses in carcinoma of the uterine cervix and hepatitis viruses in hepatocellular carcinoma. Thus far, only one bacterial species has been implicated: helicobacter pylori in gastric carcinoma [5]. It has been assessed that 17.8% of cancers globally are as a result of infectious agents, and helicobacter pylori is assessed to be accountable for 5.5% of all cancer cases and more than 60% of gastric cancer cases [6]. Even though helicobacter pylori is correspondingly occupied as a causative agent in gastric mucosa-associated lymphoid tissue lymphoma.

This article is focused on gastric adenocarcinomas, which represent more than 90% of gastric cancer cases. Other infectious agents categorized as carcinogens by the International Agency for Research on Cancer (IARC) are: Epstein-Barr virus (EBV or HHV4) in lymphomas and nasopharyngeal carcinoma, herpes virus 8 (HHV8) in Kaposi's sarcoma, Schistosoma haematobium in bladder carcinoma, human T-cell lymphotropic virus type I (HTLV-1) in adult T-cell leukemia lymphoma, and Opistorchis viverrini in cholangiocarcinoma [7]. Moreover, chronic inflammation is known as a risk factor for increasing numerous types of cancer, containing gastric, esophageal, intestinal, prostate, and others [8]. Macrophages, dendritic cells, and lymphocytes are effectors of the inflammatory role in the initiation and promotion of the neoplastic procedure, regularly mediated by cytokines and chemokines [9]. This article briefly summarizes the main aspects concerning gastric adenocarcinomas and the carcinogenic effects of HELICOBACTER pylori infection.

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Table (1): New cases and deaths from cancer by site worldwide

	New Cases	Deaths
Lung	1,608,800	1,378,400
Breast	1,383,500	458,4
Colon and rectum	1,233,700	608,6
Stomach	989,600	738
Liver	748,000	695,9
Prostate	913,800	258,4
Cervix uteri	529,400	274,9
Esophagus	482,300	406,8
All cancers (excluding non-melanoma skin cancer)	12,677,900	7,571,500

Epidemiological Aspects

Gastric intestinal metaplasia (GIM) is an initial step in gastric carcinogenesis, however, there is argument concerning routine surveillance of patients with GIM in regions with a low prevalence of gastric cancer [10]. In a retrospective case-control study of patients from the Kaiser Permanente Southern California district in the U.S.A., the occurrence of gastric cancer in 923 patients with GIM (median age at diagnosis, 68 years) was compared with that of an age- and gender-matched reference population. Generally, 25 patients with GIM (2.7%) developed gastric cancer and in 17 of them (70%), gastric cancer was diagnosed at the same time as gastric intestinal metaplasia. The other eight cases of gastric cancer were identified within a median time period of 4.6 years after diagnosis of GIM. Family history and extensive intestinal metaplasia were related with an enlarged risk of subsequent gastric cancer. Consequently, surveillance of patients with the stated risk criteria can increase early recognition of gastric cancer.

In a Korean case-control study on 514 patients determined to have alcoholic liver illness and control subjects coordinated for age, gender, and body mass index who experienced esophagogastroduodenoscopy (EGD) screening for gastric neoplasia, the chances of distinguishing a gastric cancer in patients with alcoholic liver illness were roughly five times more than in the sound controls [11]. Alcoholic liver illness was observed to be a free hazard factor for gastric cancer by multivariate calculated examination.

No critical contrasts were seen in the pervasiveness of helicobacter pylori, gastric adenoma and gastric cancer between patients with alcoholic liver illness and those with nonalcoholic steatohepatitis (NASH). In addition, Korean case-control study reported that the occurrence of gastric adenoma and gastric cancer in patients with colorectal cancer (CRC) and controls was evaluated (one patient: three controls) [12]. Cases were 142 patients who underwent surgery after being diagnosed with CRC between 2004 and 2013 at Chungnam National University Hospital while 426 randomly selected age- and gender-matched subjects who were negative for CRC and colon polyps throughout health screening attended as controls. Patients and controls experienced follow-up by upper gastrointestinal endoscopy. Gastric adenoma or gastric cancer occurred significantly more often in patients with colorectal cancer than in the controls (25% vs. 5%, respectively). Alcohol history and poor differentiation of colorectal cancer were both found to be associated with a six fold increased risk of gastric adenoma or gastric cancer.

This highlights the relevance of screening based on upper gastrointestinal endoscopy in Korean patients with colorectal cancer, particularly those with a history of alcohol consumption and poor cancer differentiation, even if no lesions are prominent in the upper gastrointestinal tract at colorectal cancer diagnosis. A population-based analysis using the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database from nine registries covering 9.5% of the U.S. population quantified the population-risk of developing gastric cancer following breast cancer (BC) [13].

Gastric cancer incidence following a ductal or lobular BC was separately compared to incidence in the general U.S. population. With respect to ductal BC, gastric cancer rates were similar to the general population. However, a history of lobular BC significantly increased the risk of gastric cancer in women aged 40-44 years, who were those carrying the highest risk. Further studies are warranted to determine the role of helicobacter pylori, treatment for breast cancer, and genetics (familial gastric cancer syndromes) in increasing the risk of auxiliary gastric cancer in this population.

Classification and Pathology of Gastric Adenocarcinomas

Gastric adenocarcinoma is a heterogeneous disease. The most frequently used classification

system in the US is the Lauren classification [14], which identifies two main histologic types: intestinal and diffuse. Ten to 15% of gastric adenocarcinomas are mixed, containing features of both types.

Even though these two types seem to follow different precancerous procedures and display clinical and epidemiologic differences, helicobacter pylori infection is the toughest risk factor for the improvement of most tumors of both types. Intestinal adenocarcinoma is the major type in populaces with high occurrence rates of gastric cancer and is the type of tumor accompanying with the worldwide drop in gastric cancer rates.

This tumor type displays a male predominance (male/female ratio of 2:1) and most cases are diagnosed throughout the sixth to eight decades of life. Meticulously, intestinal-type adenocarcinomas are composed of cohesive tumor cells forming unbalanced glandular or papillary structures, or they might be organized in sheets in a solid pattern. Diffuse-type adenocarcinomas do not display gender predominance, tend to grow in younger subjects, have a lesser prognosis than the intestinal-type tumors, and are more commonly placed in proximal stomach than in distal stomach.

While environmental factors seem to play a less vital role than in the intestinal-type tumors, helicobacter pylori infection is likewise connected with the improvement of diffuse-type adenocarcinomas [15]. Notwithstanding the overall drop in gastric cancer rates, the proportion of diffuse-type carcinomas has been cumulative in several countries [16]. Microscopically, diffuse-type gastric adenocarcinomas are tranquil of non-cohesive, poorly distinguished, tumor cells that disseminate individually or in small clusters insightful the stroma. A subtype, the signet-ring cell adenocarcinoma, is made by characteristically round tumor cells comprising abundant intracytoplasmic mucin and nuclei flattened against the periphery of the cells.

Nearly 10% of gastric adenocarcinomas have familial clustering. Hereditary diffuse gastric cancer is a cancer predisposition syndrome related with germline mutations and with methylation of the gene encoding for E-cadherin (CDH1), a protein for cell-to-cell adhesion that plays a significant role in the conservation of cell polarity in epithelial tissues [17]. Even though gastric cancer cases allied to this syndrome account for less than 1% of the total cases of gastric cancer, it is of great clinical significance as a result of the early onset (mean age at diagnosis 40 years) and high penetrance. The syndrome is controlled by the improvement of multiple independent foci of diffuse-type gastric adenocarcinoma, regularly with signet-ring cell morphology. Prophylactic total gastrectomy is the suggested treatment for patients with germline CDH1 mutations to remove the risk for developing gastric adenocarcinoma [18].

Screening and Prevention

The effectiveness of a serologic biopsy has been challenging as a result of high variations in accurateness in different areas of the world. A population-based multiphase study was conducted by Tu et al. where gastric cancer risk was evaluated in 12,112 participants of a Gastric Diseases Screening Program with prospective follow-up by gastroscopy and measurement of the five stomach-specific serologic biomarkers: pepsinogen I (PGI), pepsinogen II (PGII), PGI/II ratio, anti-helicobacter pylori antibody, and gastrin-17 (G-17).

A cross-sectional analysis, a follow-up analysis, and an integrative risk estimation modeling analysis were performed. In the cross-sectional analysis, the serologic biomarkers (especially PGII, the PGI/II ratio, and helicobacter pylori seropositivity) were associated with the occurrence of precancerous gastric conditions, intra-epithelial neoplasia or gastric cancer at enrollment. In the follow-up analysis, low PGI levels and PGI/II ratios were related with a higher risk of increasing gastric cancer, while both low and high G-17 levels were allied with a higher risk of increasing gastric cancer. In the risk prediction modeling analysis, the five biomarkers combined improved prediction beyond traditional risk factors and identification of precancerous lesions at enrollment. Additionally, higher serologic biopsy scores based on the five biomarkers at admission were related with a higher risk of increasing gastric cancer throughout follow-up. Therefore, a serologic biopsy based on the five biomarkers could be used to recognize high-risk individuals for additional diagnostic gastroscopy, and to stratify an individual's risk of increasing gastric cancer to guide targeted screening [19].

The corpus-predominant gastritis index is a primary histologic marker to recognize helicobacter pylori-infected gastric cancer relatives at risk of gastric cancer. In a case-control study by Cheng et al. [20], the prevalence of corpus-predominant gastritis index was assessed in Taiwanese patients with no ulcer dyspepsia (NUD, N=349) as well as in control patients with duodenal ulcer (DU, N=224).

Patients with NUD had higher prevalence rates of corpus-predominant gastritis index than controls (47.0% vs 29.9%, P<.001), particularly after the age of 40 years. Operative link on gastric atrophy (OLGA) and intestinal metaplasia assessment (OLGIM) stages III/IV were also more prevalent in

patients with NUD than in controls. NUD patients with corpus-predominant gastritis index had a threefold increased risk of spasmolytic polypeptide-expressing metaplasia (SPEM), particularly after the age of 55 years. Serum pepsinogen I/II ratio was significantly lower in patients with corpus-predominant gastritis index than in those without corpus-predominant gastritis index.

Gastroscopy with biopsies performed 1 year after eradication showed a significant regression of corpus-predominant gastritis index, whereas no histologic regression was observed for patients with SPEM and OLGA/OLGIM stage III/IV. The authors concluded that corpus-predominant gastritis index might aid as a histologic marker earlier than OLGA/OLGIM for increased gastric cancer risk. As corpus-predominant gastritis index was the only histologic marker regressing after helicobacter pylori eradication, patients with corpus-predominant gastritis index but no advanced preneoplastic conditions can be those with the highest gastric cancer risk lessening after eradication therapy.

Gastric Cancer: Biomarkers for Treatment Response

Perioperative chemotherapy develops whole survival in patients with gastric cancer and locoregional illness. Nonetheless, the recognition of patients susceptible to disease relapse residues challenging. In a secondary post hoc analysis of the MAGIC trial, pathologic tumor response and lymph node status of 330 patients with gastric cancer (including patients with junctional cancers) who experienced perioperative chemotherapy were analyzed [21].

Resection samples were scored for pathologic response using the Mandard tumor regression grading (TRG) method. TRG 1 was referred to as complete tumor regression, while TRG 5 designated a lack of regression after neoadjuvant cytostatic treatment. Whereas univariate analysis presented better survival in patients with pathologic tumor regression (TRG 1 or 2), multivariate analysis revealed lymph node metastases as the only independent factor expecting overall survival (HR 3.36, 95% CI, 1.70-6.63).

A supplementary secondary post hoc analysis of the MAGIC trial assessed the advantage of cytostatic treatment for patients with gastric cancer and locoregional illness regarding the microsatellite instability status [22]. Microsatellite instability outcomes were obtainable for 303 patients, 20 of them had high microsatellite instability. When treated with surgery alone, no significant difference in general survival was revealed between MSS and high microsatellite instability /mismatch repair deficient (MMRD) tumor patients. Remarkably, perioperative chemotherapy even led to an enlarged mortality risk in high microsatellite instability patients (HR 2.18, 95% CI, 1.08-4.42), therefore reinforcement indication of a poor responsiveness to chemotherapy in these patients.

Gastric mucosa-associated lymphoid tissue lymphoma

Gastric mucosa-associated lymphoid tissue lymphoma (GML) is thoroughly related to helicobacter pylori infection. In a retrospective assessment of 144 consecutive patients admitted with GML (1993-2013), eradication treatment was highly operative in inducing complete remission (CR) and long-term prognosis was very satisfactory. At stage EI, 92% of patients received a helicobacter pylori eradication treatment; 83% achieved CR after a mean period of 7 months, and 86% remained in CR after a mean follow-up time of 105 months. Helicobacter pylori infection was allied with higher CR rates whereas patients with lymphoma contained to the antrum plus body had lower CR rates. Relapse occurred in 14% of the patients after a mean period of 21 months. Relapse rates were higher in patients with helicobacter pylori re-infection, more than one eradication regimen, and lymphomas localized in the corpus. Regarding stage EII, only 30% of patients getting helicobacter pylori eradication experienced CR. Among 16 patients diagnosed at stage EIV, nine achieved CR after chemotherapy ± surgery and 3 of 7 without remission died as a result of disease progression. The 5- and 10-year overall disease free survival rates were 90.5% and 79.1%, respectively [23]. In another retrospective study, the effectiveness of helicobacter pylori eradication treatment was assessed in 345 Korean patients with GML, irrespective of the helicobacter pylori infection status or disease stage. Helicobacter pylori infection was noticed in 317 of 345 patients (91.9%). The CR rate after eradication treatment was expressively higher in helicobacter pylori-positive patients than in helicobacter pylori-negative patients (84.5% vs 57.1%). CR rates after eradication were 83.3% for stage IE1 and 74.4% or above for stage IE2. Therefore, the authors concluded that eradication therapy is valuable as an initial treatment for GML, regardless of the helicobacter pylori infection status and stage [24].

Numerous authors reported that a high percentage of early-stage gastric drawn-out large cell B lymphomas residues helicobacter pylori-dependent. Prominently, drawn-out large cell B lymphomas can probably be preserved by helicobacter pylori eradication. Though, dissimilar mucosa-associated lymphoid tissue lymphoma,

drawn-out large cell B lymphomas may progress rapidly if it is unresponsive to helicobacter pylori eradication.

Therefore, identifying markers that may predict a helicobacter pylori-dependent status of gastric drawn-out large cell B lymphomas is mandatory. Kuo et al.[25] from Taiwan recommended that expression of CagA and CagA-signaling molecules p-SHP2 and p-ERK in malignant B cells is allied with helicobacter pylori dependence. MicroRNAs are deregulated in lymphomas. Fernandez et al. compared the expression of 384 miRNA in a series of 10 GMLs, and found 12 chronic gastritis and two reactive lymph nodes. They found a significant overexpression of miR-142-3p and miR-155 and downregulation of miR-203 in GML as compared to gastritis. They suggested that expression levels of miR-142-3p, miR-155, and miR-203 could be useful biomarkers for the differential diagnosis between GML and gastritis [26].

Correspondingly, Floch et al. studied regulation of miRNAs in a GML mouse model using BALB/c mice thymectomized at 3 day postbirth (d3Tx model) and infected with helicobacter pylori. They found five miRNAs overexpressed in GML. They identified TP53INP1, an antiproliferative and pro-apoptotic protein, as a common target of 4 of the 5 upregulated miRNAs, suggesting these miRNAs may act in synergy to promote the development of GML [27].

CONCLUSION

Targeted surveillance of a subgroup of patients with gastric intestinal metaplasia increases early detection of gastric adenocarcinoma. Data from the secondary post hoc analysis of the MAGIC trial may have an important impact on the selection of patients who would benefit from perioperative chemotherapy. In the near future, a microsatellite instability status can be essential in patients with gastric adenocarcinoma and locoregional disease. Gastric adenocarcinoma patients with high microsatellite instability seem to be at a drawback regarding perioperative chemotherapy and can consequently go directly for surgery.

A helicobacter pylori eradication therapy was confirmed to be important as an initial treatment for gastric mucosa-associated lymphoid tissue lymphoma irrespective of the helicobacter pylori infection status and stage. The possibility to cure some cases of gastric diffuse large cell lymphoma with helicobacter pylori eradication was confirmed. The intriguing associations between both helicobacter pylori infection, chronic atrophic gastritis and CRC warrant further evaluation.

The study was done after approval of ethical board of Princess Nourah university.

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