THE ROLE OF HELICOBACTER PYLORU IN CANCER OF CARDIOESOPHAGEAL ZONE

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Abstract. *Esophageal cancer ranks the eighth in the world's cancer incidence and the sixth in the global cancer death cause. There are two major histological subtypes of the esophagus: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Esophageal cancer is mainly a disease of the male population over 55 years of age. Men get sick more often than women on average 5-10 times. The peak incidence occurs at the age of 55-60 and older, with people over 70 accounting for about 40 percent of cases. The highest incidence is observed in the so-called "Central Asian zone of esophageal cancer", which includes the Caspian coast, Central Asian republics, Mongolia and northwestern China. In the structure of cancer incidence in Uzbekistan, esophageal cancer is 3.8% in men and 3.7% in women.*

Keywords: *Helicobacter Pylori, Cardioesophageal cancer, Proinflammatory genotypes.*

Introduction

Gastoesophageal junction (CEJ) cancer, especially adenocarcinoma of the CEJ, represents a solid tumor entity with a rapidly increasing incidence in Western countries during recent decades [25,10]. Being anatomically associated with esophageal cancer and gastric cancer, CEJ cancers, which are predominantly considered to be adenocarcinomas, are increasingly being considered as a distinct tumor entity. They have a constellation of risk factors that are distinct from those for esophageal and gastric cancers, with a certain genetic configuration and principally tailored therapeutic approaches. In Western countries, where the highest incidence of CEJ cancer is found, a limited level of centralization leads to difficulties in recruitment for prospective studies. In Asian countries, especially in Korea and Japan, the incidence of CEJ cancer is not high compared with gastric cancer, for which a large number of clinical trials have been performed, and the surgical treatment is highly standardized [40,25].

According to the Cancer Register of the Republican Cancer Research Center in Uzbekistan, cancer esophagus (15.1%) has a significant role in the incidence of cancer, along with breast cancer (20.4%), neoplasms of the cervix (13.1%), stomach (8.5%), ovaries (5.4%), lungs (4.1%), lymphoma (4 , 1%), lips, oral cavity, pharynx (3.3%), central nervous system (3.1%), rectum (2.8%), bones and soft tissues (2.7%), skin (2,5%), colon (2.4%), leukemia (2.4%), kidney (1.9%), bladder (0.85%), larynx (0.78%).Mortality from esophageal cancer in 2019 averaged 1.1%. Helicobacter pylori is a common bacterium in the upper digestive tract, which infects about half of the world [12] Marshall and Warren first reported the cultivation of Helicobacter pylori from human gastric mucosa in 1983 [6]. The International Agency for Research on Cancer and the World Health Organization believed that Helicobacter pylori is a carcinogen of gastric cancer. However, some studies have shown that Helicobacter pylori infection is negatively correlated with some diseases. The primary pathogenic role of *H. pylori* in peptic ulcer formation is supported by

robust evidence [33], and *H. pylori* was recognized as a true class I carcinogen for gastric cancer by the International Agency for Research on Cancer and the World Health Organization in 1994 Helicobacter pylori infection appeared to have a "protective effect." Since the 20th century, the prevalence of Helicobacter pylori hasdeclined in Western countries; At present, the relationship between Helicobacter pylori and esophageal squamous cell carcinoma has not been clearly explained; the evidence of its protective or harmful effects on esophageal adenocarcinoma is still contradictory. In recent years, articles on the relationship between Helicobacter pylori and esophageal cancer have been published in succession; new data can be used to further analyze the relationship between Helicobacter pylori and esophageal cancer [38].

Risk factors of esophageal cancer

Demographics. It has been reported that there is an increased risk of esophageal adenocarcinoma diagnosis for persons older than 50 years, but no trend was found for an increased magnitude of risk beyond age 50 years.[7]. Racially white individuals have a 2-fold risk of developing esophageal adenocarcinoma than Hispanics, and a 3e4-fold increased risk when compared with Blacks.[20].A prevalence study performed in the United States on Barrett's esophagus through the use of an endoscopy indicated that its prevalence among non-Hispanic whites was 6.1%, compared to 1.7% among Hispanics and 1.6% among Blacks. Therefore, much of the differences in cancer risk attributable to race ethnicity may be the reason for the differences in the risk of being diagnosed with Barrett's esophagus.[1]. Additionally, the male/female ratio of Barrett's esophagus patients is about 2:1. However, the incidence rate of esophageal adenocarcinoma shows a 38-fold increase in males over females, which may suggest that men are not only more likely to develop Barrett's esophagus, but also once they have it, may b more likely to then have their diagnosis progress to cancer.[13].

Smoking. Smoking is a risk factor associated with both Barrett's esophagus and esophageal adenocarcinoma. It has been reported that current smokers have an increased risk of esophageal adenocarcinoma, as compared to nonsmokers [odds ratio (OR)Z1.96; 95% confidence interval (CI), 1.64e2.34] [14]. Sex and duration of smoking cessation are also associated as risk factors of esophageal adenocarcinoma. Men with a history of smoking had a slightly higher risk of esophageal adenocarcinoma (ORZ2.10; 95% CI,1.71e2.59) than women (ORZ1.74; 95% CI, 1.21e2.51). Persons who had quit smoking cigarettes for 10 years still had an increased risk of esophageal adenocarcinoma when compared to those who had never smoked (ORZ1.72; 95% CI, 1.38e2.15). Continuing to smoke also enhances the risk of Barrett's esophagus progressing to cancer.[26].Smoking was also a major cause in ESCC, where the OR was 2.9 (95% CI, 2.1e4.1); the OR in men was higher than in women (4.0 vs. 2.7, respectively). A current smoker has more risk than an ex-smoker. Total packs per year smoked was also correlated with increasing risk of ESCC. For those who smoked > 30 packs per year, the OR was 4.1 (95% CI, 2.7e6.2), and the rate was higher in men than in women (5.5 vs. 4.0, respectively)[38].

Alcohol consumption. Ethanol was metabolized by alcohol dehydrogenase and formed acetaldehyde. Acetaldehyde interacted with DNA and produced DNA adducts to induce gene mutation. Thus, alcohol is one of the risk factors for the development of upper aerodigestive tract cancer.[42].The average weekly alcohol intake exceeded 170 g, and the OR was significantly increased in ESCC patients but not in esophageal adenocarcinoma patients. The OR was upregulated in men and women with ESCC who consumed more than 210 g and 70 g per week, respectively[39].

Gastroesophageal reflux disease. GERD is one of the important risk factors for both Barrett's esophagus and esophageal adenocarcinoma. Approximately 10% of patients diagnosed with GERD will develop Barrett's esophagus.[22]. Patients

experiencing recurrent heartburn or regurgitation have an approximately 5-fold increased risk to progress to esophageal adenocarcinoma, when compared to those without GERD- related symptoms.[13].

Obesity and body composition. Obesity is a risk factor toward developing esophageal adenocarcinoma. Both body mass index (BMI) and increased abdominal obesity are also associated with cancer risk. It has been reported that a BMI higher than 25 was associated with an increased risk of esophageal adenocarcinoma in both males (ORZ2.2; 95% CI, 1.8e2.7) and females (ORZ1.9; 95% CI, 1.5e2.5).[16]. The risk was also increased at greater BMI levels. Obese males and females had a higher risk of esophageal adenocarcinoma (ORZ2.4; 95% CI, 1.9e3.2 and ORZ1.9; 95% CI, 1.5e2.5, respectively) than did overweight males and females (ORZ1.8; 95% CI, 1.5e2.2 and ORZ1.5; 95% CI, 1.1e2.2, respectively). These reports suggest a dose response between the risk of esophageal adenocarcinoma and an increased BMI (p trend <0.001)[27]. However, a high BMI level significantly decreased the risk of ESCC [adjusted relative risk (RR) for top vs. bottom quintile of BMI was 0.38; 95% CI, 0.23e0.62]. The adjusted RR was 0.67 (95% CI, 0.49e0.93) for BMI 25e29.9, and 0.47 (95% CI, 0.24e0.94) for BMI 30. Unlike BMI, blood pressure had a positive correlation with risk in ESCC. Higher mid blood pressure was correlated with an increased risk of ESCC. The adjusted RR for ESCC was 2.60 (95% CI 1.54e4.39) for top versus bottom quintile of mid blood pressure.[34]. Alcohol consumption has been identified as a risk factor in ESCC, and it could also cause hypertension. Thus, alcohol consumption was a confounder that could induce both hypertension and ESCC. Persistent *H. pylori* infection is believed to promote the development of gastric cancer through the development of atrophic gastritis and decrease in gastric acid secretion. However, it has a suppressive effect on GERD, Barrett's esophagus, Barrett's esophageal adenocarcinoma, and GEJ adenocarcinoma.

In Western countries, *H. pylori* infection rates in cardiac cancers were found to be considerably lower than those in the control group. However, in Asian countries where gastric cancer is common, *H. pylori* infection rates are high in both noncardiac and cardiac cancers, and *H. pylori* infection is considered a carcinogenic risk factor for both sites of cancer [32]In a comparison of *H. pylori* infection rates between GEJ adenocarcinoma and distal gastric carcinoma [31]the *H. pylori* infection rate in GEJ adenocarcinoma was significantly lower, and the degree of histological gastritis in the gastric body was also significantly lower. In Asian countries, including Japan, where the incidence of gastric cancer is high, 2 types of GEJ adenocarcinoma have been reported: one that is not associated with *H. pylori* infection as in Western countries and another that is associated with *H. pylori* infection. McColl described the pathogenesis of GEJ adenocarcinoma in terms of gastric acid secretion and categorized it into 2 types: one that is associated with atrophic gastritis and low gastric acid secretion (similar to distal gastric cancers) and another type that is associated with excessive acid secretion with or without *H. pylori* infection (similar to esophageal adenocarcinomas) [35].

A large number of patients with chronic gastritis have undergone *H. pylori* eradication therapy in Asian countries, including Japan. It is important to determine whether the incidence of esophageal adenocarcinoma will increase after *H. pylori* eradication therapy, especially in the context of future trends of GEJ adenocarcinoma. Although there is currently no sign of an increase in the incidence of GEJ adenocarcinoma in post-eradication cases in Japan, there is only limited evidence on this issue. Take et al. [43] followed up 2,737 patients after *H. pylori* eradication therapy for an average of 7.1 years and found 2 cases of esophageal adenocarcinoma. They concluded that although the incidence of GEJ adenocarcinoma in patients after *H. pylori* eradication is higher than that in the general population, it is still very low. A previous study also found that the prevalence of esophageal adenocarcinoma is higher with persistent *H. pylori*

infection than after eradication therapy, and a recent meta- analysis suggested that *H. pylori* infection may reduce the risk of esophageal adenocarcinoma in the general population. However, these findings may be one-sided; the statement of "protection effect" may be overestimated [23]. At present, it is reasonable to assume that the widespread use of *H. pylori* eradication therapy for chronic gastritis will not directly lead to an increase in the incidence of esophageal adenocarcinoma and GEJ adenocarcinoma, although further studies are needed to clarify this important issue.

Conclusion.

Esophageal cancer remains a significant cause of all cancerrelateddeaths worldwide. With a spiked increase in incidencebeing observed in certain Western countries, 3-yearsurvival rates have been shown at rates of 10-15%. Mostpatients have already manifested the advanced disease atdiagnosis and are therefore precluded from curative surgical resection. However, identification of reliablemarkers that could predict treatment outcome is stilllimited in the available medical research literature. Thus,it is important to identify biomarkers that are able topredict any post-CCRT response in order to develop theproper treatment guidelines. We can then use these resultsto help reduce the currently high mortality rates byapplying the most beneficial treatment methods to patientsin the future. Esophageal cancer remains a lethal disease entity. The biologic characteristics of the disease have evolved from squamous cell carcinoma predominant disease to adenocarcinoma. Death rates and incidence continue to increase, especially with regard to adenocarcinoma. Recent advances in multimodality treatment show promise in improving outcomes and survival while decreasing morbidity. Proper staging and workup is vital to determine treatment strategies and goals. Once determined, a multidisciplinary approach should be employed for treatment and surveillance. Preferably, evaluation and treatment options for each patient with localized esophageal cancer should be discussed in a multidisciplinary treatment planning conference. In general, early stage T1 tumors are best managed by

endoscopic modalities (superficial T1a lesions) or esophagogastrectomy (T1b) if possible. Lesions extending into and beyond the submucosa and those with nodal involvement seen on preoperative staging should be treated with combined multimodality therapy in a high volume cancer center. Unresectable disease or patients unfit for chemotherapy, radiation therapy, and/or surgery should be considered for palliation.

References

1. Abrams JA, Fields S, Lightdale CJ, Neugut AI. Racial and ethnic disparities in the prevalence of Barrett's esophagus among patients who undergo upper endoscopy. ClinGastroenterolHepatol. 2018;6:30e34.
2. Amieva MR, El-Omar EM. Host-bacterial interactions in *Helicobacter pylori* infection. Gastroenterology 2018;134:306–323.
3. Ando T, El-Omar EM, Goto Y, et al. Interleukin 1B proinflammatory genotypes protect against gastro-oesophageal reflux disease through induction of corpus atrophy. Gut 2016;55:158–164
4. Ando T, El-Omar EM, Goto Y, et al. Interleukin 1B proinflammatory
5. Atherton JC, Blaser MJ. Coadaptation of *Helicobacter pylori* and humans: ancient history, modern implications. J Clin Invest 2019;119:2475–2487
6. B. J. Marshall and J. R. Warren, "Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration," The Lancet, vol. 1, no. 8390, pp. 1311–1315, 1984
7. Bhat S, Coleman HG, Yousef F, et al. Risk of malignant progression in Barrett's esophagus patients: results from a large population-based study. J Natl Cancer Inst. 2015;103: 1049e1057.
8. Blaser MJ. Disappearing microbiota: *Helicobacter pylori* protection against esophageal adenocarcinoma. Cancer Prev Res (PhilaPa) 2018;1:308–311.)
9. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018:

GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424. Crossref, Medline, Google Scholar

10. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. SeminRadiatOncol 2013;23:3-9. PUBMED | CROSSREF

11. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. SeminRadiatOncol. 2013;23:3-9. Medline, Google Scholar

12. C. Y. Kao, B. S. Sheu, and J. J. Wu, "Helicobacter pylori

13. Cook MB, Corley DA, Murray LJ, et al. Gastroesophageal reflux in relation to adenocarcinomas of the esophagus: a pooled analysis from the Barrett's and Esophageal Adenocarcinoma Consortium (BEACON). PLoS One. 2014;9:e103508.

14. Cook MB, Kamangar F, Whiteman DC, et al. Cigarette smoking and adenocarcinomas of the esophagus and esophagogastric junction: a pooled analysis from the international BEACON consortium. J Natl Cancer Inst. 2015;102:1344e1353.

15. Cook MB, Wild CP, Forman D. A systematic review and metaanalysis of the sex ratio for Barrett's esophagus, erosive reflux disease, and nonerosive reflux disease. Am J Epidemiol. 2015;162:1050e1061.

16. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiol Biomarkers Prev. 2008;17:352e358

17. Daugule, J. Zavoronkova, and D. Santare, "Helicobacter pylori and allergy: update of research," World Journal of Methodology, vol. 5, no. 4, pp. 203–211, 2015.–11

18. El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2014;404:398–402

19. El-Omar EM. The importance of interleukin 1beta in *Helicobacter pylori*

associated disease. Gut 2011;48:743–747

20. El-Serag HB, Mason AC, Petersen N, Key CR. Epidemiological differences between adenocarcinoma of the oesophagus and adenocarcinoma of the gastric cardia in the USA. Gut. 2012;50: 368e372

21. F. Turati, I. Tramacere, C. La Vecchia, and E. Negri, “A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma,” *Annals of Oncology*, vol. 24, no. 3, pp. 609–617, 2013.

22. Fennerty MB. Barrett’s-related esophageal cancer: has the final hurdle been cleared, now paving the way for human chemoprevention trials? Gastroenterology. 2012;122: 1172e1175.

23. Gao H, Li L, Zhang C, Tu J, Geng X, Wang J, et al. Systematic review with meta- analysis: association of Helicobacter pylori infection with esophageal cancer. Gastroenterol Res Pract. 2019 Dec 1;2019:1953497.

24. Genotypes protect against gastro-oesophageal reflux disease through induction of corpus atrophy. Gut 2016;55:158–164.

25. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al. The global burden of cancer 2013. JAMA Oncol 2015;1:505-527. PUBMED | CROSSREF

26. Hardikar S, Onstad L, Blount PL, Odze RD, Reid BJ, Vaughan TL. The role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: a prospective study of Barrett’s esophagus. PLoS One. 2013;8:e52192

27. Hoyo C, Cook MB, Kamangar F, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol. 2012;41:1706e1718.

28. Independent of environmental and genetic modifiers. Gastroenterology. 2013;139:73– 83.)

29. J. Ferlay, I. Soerjomataram, R. Dikshit et al., “Cancer incidence and mortality

worldwide: sources, methods and major patterns in GLOBOCAN 2018" International Journal of Cancer, vol. 136, no. 5, pp. E359–E386, 2018

30. J. H. Rubenstein and J. B. Taylor, "Meta-analysis: the association of oesophageal adenocarcinoma with symptoms of gastro-oesophageal reflux," *Alimentary Pharmacology & Therapeutics*, vol. 32, no. 10, pp. 1222–1227, 2014.