The Relative Frequency of Helicobacter Pylori Infection in Proximal and Distal Gastric Carcinomas

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ABSTRACT

Objectives:
To find out the relative frequency of *H. pylori* infection in proximal and distal gastric adenocarcinomas and to determine its relationship with other environmental and familial factors responsible for gastric carcinogenesis.

Methodology:
This cross sectional study was conducted on Afghani patients with gastric cancer. A total of 72 gastric adenocarcinoma patients, with equal number (36) of proximal and distal gastric cancer, were enrolled from Northwest General Hospital & Research Center and Rehman Medical Institute, Peshawar. After informed written consent multiple gastric biopsies were taken from all the patients and were processed. Sections were stained with H&E and Giemsa for histology and *H. pylori* detection respectively.

Results:
The overall frequency of *H. pylori* was 29.2% (21/72) with no statistically significant difference (p=0.346) between proximal (48.2%) and distal (57.1%) gastric adenocarcinoma. Males were more affected by *H. pylori* associated cancers. Proximal tumors were more common in the younger age group and distal tumors in the older age group. A higher frequency of tobacco use, intake of high salty diet in combination with a high temperature diet were found to be more related to proximal gastric tumors. No significant difference was observed regarding the main histological types of gastric adenocarcinomas among the proximal and distal gastric tumors and also in their relation to *H. pylori* infection.

Conclusion:
H. pylori infection is equally common in the proximal and distal gastric adenocarcinomas in the Afghani patients with gastric cancer especially on the north eastern border near to Pakistan. Proximal gastric tumors are more associated with tobacco use and dietary factors.

Key words:
Helicobacter pylori, frequency, gastric adenocarcinoma, proximal gastric cancer, distal gastric cancer, dietary factors

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INTRODUCTION

Over most of the 20th century, the worldwide leading cause of cancer related deaths has been the adenocarcinoma of stomach. It is ranked second to lung cancer, with an estimated 875,000 new cases diagnosed annually around the globe and is the 3rd leading cause of mortality from cancer in both sexes (723,000 deaths, 8.8% of the total).[1] The estimated mortality rate from gastric cancer in Pakistan has been 8 and 3 per 100,000 in men and women respectively.[2] In many areas around the world, incidence of this cancer has gradually decreased, mainly due to the dietary changes, improved hygiene, different food preparatory methods and environmental factors.[1] Gastric cancer is related to risk factors like high salt intake, drinking alcohol and tobacco smoking. Risk of gastric cancer development is very high among individuals with *Helicobacter pylori* (*H. pylori*) infection. International agency for research on cancer (IARC) consensus group and World Health Organization (WHO) in 1994 stated that enough histologic and epidemiologic evidence existed to label *H. pylori* as a definite carcinogen.[3] *H. pylori* infection has been considered as an important risk factor for adenocarcinoma of esophagogastric junction (EGJ) in case of the proximal stomach tumors, while in case of distal esophageal cancer, gastroesophageal reflux disease

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disease (GERD) is known to be a major risk factor.[4]

In total, the distal part of the stomach is the region with most cases of gastric adenocarcinoma. Although gastric carcinoma incidence has decreased as a whole, but in recent decades proximal gastric cancers have increased.[5]

H. pylori infection and proximal stomach cancer have a positive correlation with each other.[6] Gastric cancer of the cardia has a strong positive correlation with *H. pylori* infection and *H. pylori* infection is regarded as a pre-cancer factor of grave importance. In contrast, proximal gastric cancers and *H. pylori* infection have been shown to have a weaker correlation in western countries.[7]

It is now very evident that *H. pylori* infection has important role in proximal gastric cancers along with the distal gastric cancers.[8] The prevalence of *H. pylori* in overall gastric carcinoma has been observed to be 60%-70% in Pakistan.[9]

The aim of this study is to investigate the relative frequency of *H. pylori* infection in people with proximal gastric carcinoma in comparison with distal gastric cancer, and to determine its relationship with other environmental and familial factors responsible for gastric carcinogenesis.

METHODOLOGY

This cross-sectional study was conducted on Afghani patients with gastric cancer especially on the north eastern border near to Pakistan. The study population comprised of 72 gastric adenocarcinoma patients with equal number (36) of proximal and distal gastric cancer, enrolled from Rehman Medical Institute (RMI) and North West General Hospital & Research Center (NWGH & RC), Peshawar, from April 2014 to September 2015. Ethical committee approval was taken from Khyber Medical University. Informed consent was obtained from all the patients. Convenient sampling technique was adopted. Patients of all age groups and both sexes with gastric cancers were selected. Multiple endoscopic biopsies were taken from the patients and analyzed further in histopathology laboratory at IBMS, KMU. Patients with upper GI complaints and undergoing endoscopy were included in the study. Patients who had been on *H. pylori* eradication treatment for too long and those with a diagnosis other than adenocarcinoma of stomach were excluded from study. The biopsy samples underwent the usual routine processing techniques in histopathology laboratory IBMS, KMU. Sections were made and stained with Hematoxylin & Eosin and Giemsa stain for microscopic observation.

The data was analyzed with statistical package for social sciences (SPSS Version 16). Calculations were done for frequencies, percentages and ratios. Chi square test was used for testing significance of frequencies between the groups. P value of ≤ 0.05 was considered as statistically significant.

RESULTS

The overall *H. pylori* infection in gastric cancer was 29.2%, while majority of the cases (70.8%) were having no *H. pylori* infection (Table-I). Slightly higher frequency of *H. pylori* infection was observed in the distal tumors (33%) as compared to the proximal tumors (25%). Males were observed to have a higher frequency of gastric cancers (2:1 male to female ratio), while the frequency of *H. pylori* infection was found to be 29% in both of the genders (Table-I). A slightly high frequency of *H. pylori* infection was observed in patients aged 51-60 years (p=0.067).

Majority of the tumors were of Lauren's diffuse-type adenocarcinoma i.e 47.2% as compared to the intestinal-type, which were present in 38.9% of the cases. Mixed-type adenocarcinomas were only found in 13.9% of the cases. A higher frequency of *H. pylori* positivity (32%) was seen among the intestinal type tumors, while among the diffuse type tumors 26% were positive for *H. pylori* infection.

Frequency of Cancer patients with a history of high salt diet intake was 47.2%, high salt diet alongwith high temperature foods intake were 30.6% and only 11.1% patients were having a history of high temperature foods/liquids consumption only. (Table-I)

Among the proximal gastric adenocarcinomas, frequency of Gastroesophageal junction (GEJ or Cardia) adenocarcinomas was the highest (31.9%). Fundus cancers were present in 11.1% of patients. Only 6.9% of cancers in proximal region of stomach were present in upper 1/3rd of body of stomach. Almost 63% positivity for *H. pylori* was seen among the fundal adenocarcinomas. (Table-I)

The moderately differentiated adenocarcinoma subtype of intestinal-type tumors was present in majority i.e. 25% of the cancers. The poorly differentiated adenocarcinoma, a subtype of diffuse adenocarcinomas, and Signet Ring cell adenocarcinoma, a subtype of diffuse adenocarcinomas, were the next common types of tumors among the patients i.e. 18.1% each. Only 9.7% of the cancers were moderate to poorly differentiated adenocarcinomas which belong to a subtype of mixed tumors. Poorly differentiated adenocarcinomas comprised of more than 50% of Signet Ring cells, a subtype of diffuse tumors was found in 11.1% of the cancer patients.

Parameters	Frequency (%)	*H. pylori positive*	*H. pylori negative*
Tumor location			
Proximal tumor	36 (50)	9 (25%)	27 (75%)
Distal tumor	36 (50)	12 (33%)	24 (67%)
Gender			
Male	48 (66.7)	14 (29%)	34 (71%)
Female	24 (33.3)	7 (29%)	17 (71%)
Tobacco Use			
Snuff + NSAIDs	5 (6.9)	1 (20%)	4 (80%)
Snuff	10 (13.9)	0 (0%)	10 (100%)
Smoking	11 (15.3)	1 (9%)	10 (91%)
NSAIDs	10 (13.9)	4 (40%)	6 (60%)
Smoking + Snuff	9 (12.5)	1 (11%)	8 (89%)
Smoking + NSAIDS	3 (4.2)	1 (33%)	2 (67%)
Diet			
Meat & Salty diet (high salt diet)	34 (47.2)	7 (23%)	24 (77%)
Hot Foods	8 (11.1)	2 (25%)	6 (75%)
High Salt diet + Hot foods	22 (30.6)	5 (22%)	18 (78%)
Proximal Location			
Fundus	8 (11.1)	5 (63%)	3 (38%)
GEJ, Cardia	23 (31.9)	5 (22%)	18 (78%)
Upper 1/3rd of body of Stomach	5 (6.9)	0 (0%)	5 (100%)

Table-I: General Characteristics of the Patients with gastric adenocarcinomas and H. pylori infection status in different groups

Proximal tumors were more common in the older age group (60±9.508 years), while the distal tumors were commoner among the younger age group (53.42±14.760 years) (p=0.052).

Patients with proximal gastric tumors were more frequent consumers of high salt diet along with Hot Foods as compared to the distal group of cancers. The difference was not significant (p=0.080). Comparison of proximal and distal gastric adenocarcinomas with regards to blood group shows that patients with proximal tumors had a predominant blood group O (p=0.017), while patients with distal tumors were having a higher frequency of blood group B (p=0.042). (Table-II)

Parameters	Tumor Location		p.value
H. pylori	**Proximal tumor**	**Distal tumor**	
Positive	9	12	0.436
Negative	27	24	
Diet			
Meat and Salty diet (high salt diet)	15	19	0.124
Hot Foods	4	4	0.721
High Salt diet + Hot foods	15	7	0.080
Blood Group			
O	12	4	0.017
A	13	14	0.807
B	4	11	0.042
AB	7	7	--

Table-II: Comparison of Proximal and Distal gastric adenocarcinomas on the basis of *H. pylori* infection status, presenting complaints, family history, dietary habits and blood groups

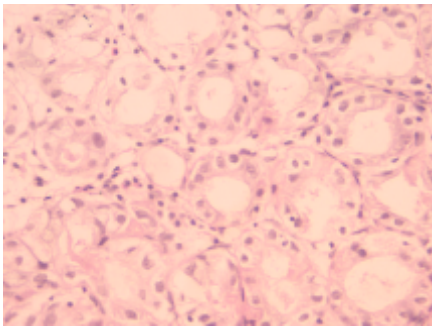

Figure 1: Photomicrograph of representative cases of well differentiated Adenocarcinoma of stomach showing glandular pattern. The inflammatory cells, lymphocytes are also seen and cytologic atypia is noted in epithelial cells (H&E 400X)

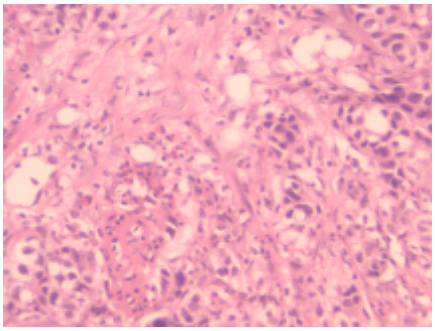

Figure 2: Photomicrograph of representative cases of diffuse Signet Ring cell Adenocarcinoma on a higher magnification. Signet Ring shaped cells with peripherally displaced nuclei are visible (H&E400X)

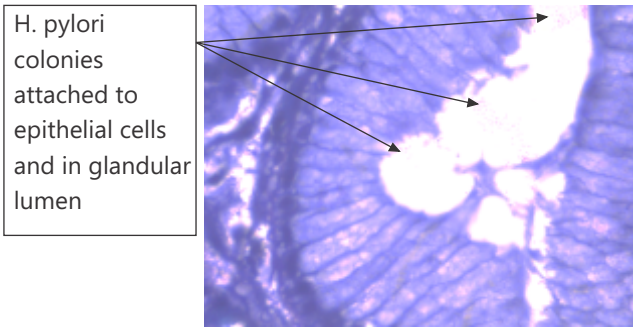

Figure 3: Photomicrograph of representative cases of moderate to poorly differentiated adenocarcinoma of stomach with H. pylori colonies visible in gastric glandular pits (Giemsa stain 1000X)

DISCUSSION

The role of *Helicobacter pylori* infection and other synergistic factors in distal gastric cancer as one of the most important risk factors of gastric cancer has been proved but its role in proximal gastric cancer is controversial. In recent decades, the incidence of proximal cancers has increased. The aim of the study was to survey the relative frequency of *H. pylori* infection in the people with proximal cancer and to compare it with this infection frequency in the distal cancer plus the role of other contributing factors in carcinogenesis.

Association of gastric cancer with *H. pylori* infection was found to be 29.2%. The result is coinciding with the study by Qureshi MA et al.[10] who reported a 34% association with *H. pylori*. An association of 29.2% of gastric adenocarcinomas with *H. pylori* in my study is much higher than that of Majid et al. (2009), who reported 15.71% of gastric adenocarcinoma patients to be histologically positive for *H. pylori* bacteria.[11] A 2:1 male to female ratio for *H. pylori* associated gastric adenocarcinomas in this study is similar to the studies by Afridi et al.[12] and Qureshi et al.[10] in the region, who have reported a 2:1 male to female ratio for this category of tumors.

In this study association of proximal and distal gastric adenocarcinomas with *H. pylori* was slightly different. This shows that proximal gastric adenocarcinomas were the result of *H. pylori* infection by a mechanism similar to distal gastric adenocarcinomas as mentioned by Correa et al.[13] and Mukaisho et al.[14] The reason is the shift in colonization of *H. pylori* from distal part of stomach with atrophic gastritis to the proximal part of stomach and also the gastric cardia in patients with *H. pylori* infection.[14] A positive strong association between *H. pylori* infection and adenocarcinomas of the non-cardia region has been observed in several studies.[7] On the other hand, a negative association of cardia adenocarcinomas with *H. pylori* infection has been strongly observed. There is a significant geographic variability in the association of *H. pylori* infection with cardia cancers throughout the world. Yamada et al. stated that in the Asian countries especially, *H. pylori* associated atrophic gastritis is responsible for a part of gastric cardia adenocarcinomas.[15] It has been proposed for long that there are two distinct etiologies of gastric cardia adenocarcinomas. One type of cardia cancer arises from severe atrophic gastritis secondarily to *H. pylori* infection and is either of the intestinal subtype or the diffuse subtype similar to the non-cardia region cancers. While the other type of gastric cardia adenocarcinomas are gastroesophageal reflux disease related and are mostly of intestinal subtype resembling more or less the esophageal adenocarcinomas.[16] This study reports that there is no difference in prevalence of *H. pylori* infection among the proximal and the distal gastric adenocarcinomas (25% in proximal and 33% in distal) which is in accordance with the study by Bornschein et al.[8]

The use of snuff (smokeless tobacco, naswar) is common among afghani people and many traditional brands are available for use by men and even some women. In this study a significant proportion of Afghani population with proximal gastric cancers were attributed to use of snuff (naswar) in contrast to the distal gastric cancers. This result is similar to the report by Gonzalez et al. in a big prospective research across Europe (EPIC study), which reported a relation between gastric cancer and tobacco use (cigarette smoking) particularly in the cardia region of the stomach.[17]

A high salt diet (meat diet was also used as a surrogate for salt exposure) was found to be associated with gastric cancers to some extent in the Afghani population in this study. Similar results were recorded by Pourfarzi et al.[18] and World Cancer Research Fund.[19] In the study by Yassibas et al.[20] have confirmed the independent role of salt and salty foods in gastric carcinogenesis. Correa's model has proposed that salt is responsible for causing irritation and damage to the gastric mucosa along with superficial gastritis which will change into atrophic gastritis and thus gastric neoplasia will be the final outcome. Salt increases the mutation causing potential of certain N-nitroso compounds alongwith the increase in cellular replication.[13]

Hot foods (either solid or liquid) were associated with gastric cancers to an extent in this study, especially when hot food was consumed alongwith a diet high in salt content. These cancers were more in the proximal stomach which indicates that the hot foods/beverages may contribute to carcinogenesis via thermal irritation of the mucosal epithelial cells in proximal stomach.[21] This may also

be attributed to the synergistic effect of these environmental factors in gastric carcinogenesis.

An increased frequency of cardia/GEJ cancers has been reported in Afghani population in this study. Pourfarzi et al. have also reported the increased incidence of gastric cardia adenocarcinomas in Ardabil, Iran.[20] The Cardia/GEJ adenocarcinomas seem to be rising all around the globe, especially in western countries nowadays. Qurieshi et al.[12] in their research in Kashmir, have reported a shift in trend towards proximal gastric adenocarcinomas. Afridi et al. have also reported in their study in Pakistan that the cardia cancers are rising in numbers.[14]

The major histological subtype among the gastric tumors was the moderately differentiated adenocarcinomas (intestinal type) followed by the poorly differentiated adenocarcinomas and Signet Ring Cell adenocarcinomas (both of diffuse type). This observation is opposite to that of Qurieshi et al. who reported the well to moderately differentiated adenocarcinomas (intestinal type) as the predominant type of tumors, followed by the poorly differentiated adenocarcinomas (diffuse type) as the second commonest type of gastric neoplasia in their study.

CONCLUSIONS

H. pylori infection is equally common in the proximal and distal gastric adenocarcinomas in the Afghani patients with gastric cancer with no gender preference in these Afghani patients especially on the north eastern border near to Pakistan. Proximal gastric tumors are more associated with tobacco use and dietary factors like hot foods especially when consumed with a high salt diet as is usually observed in this population. An increased incidence of GEJ/Gastric Cardia tumors among the proximal gastric tumors has been observed in this study.

RECOMMENDATIONS

Eradicating *Helicobacter pylori* infection can be effective in preventing the distal gastric cancers in addition to preventing the proximal gastric cancers. *H. pylori* eradication regimens should be implemented strictly for preventing gastric cancers. Regular screening of susceptible population for *H.pylori* infection is necessary in our part of the world for which purpose latest diagnostic techniques should be introduced as early as possible. Also further research is warranted to understand the pathogenesis of gastric cancer due to *H. pylori* infection and other risk factors mentioned in this study

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