Case Control Study

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H. pylori infection and gastric cancer in Bangladesh: a case-control study

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Background: Like that of other Asian countries gastric cancer (GC) is also a leading cancer in Bangladesh and also a cause for cancer-related mortality. Infection with *Helicobacter pylori* (*H. pylori*) is the strongest recognized risk factor for gastric adenocarcinoma. The infection is also prevalent in common people. This case-control study was carried out to find an association between GC and *H. pylori* infection in the community.

Materials and Methods: To evaluate association of *H. pylori* and carcinoma of stomach this study was conducted at National Institute of Cancer Research & Hospital, Dhaka from January 2013 to December 2014. *H. pylori* status was determined serologically by using *H. pylori* kit in the department of Biochemistry laboratory of Bangabandhu Sheikh Mujib Medical University. In total, 114 patients with GC and 520 patients not having GC were studied as controls. Logistic regression method was used to calculate the odds ratio.

Results: Significantly more patients in the case group (86.8%) were found to be seropositive for *H. pylori* antigen in contrast to the control group (67.5%). All of the cases in the present study were in advanced stage. No significant association between *H. pylori* seropositivity and tumor location was found. It was noted that undifferentiated gastric carcinoma had slightly more association with *H. pylori* infection. Younger *H. pylori*–infected patients had been found to be at higher relative risk for GC than older patients.

Conclusion: As there is a strong association found between GC and *H. pylori* infection special emphasis to eradicate *H. pylori* infection might reduce the incidence of this dreadly disease.

Keywords: Gastric cancer, *H. pylori* infection, Case-control study

Gastric cancer (GC) is one of the important malignancies that causes widespread morbidity and mortality. Like that of other Asian countries GC is also a leading cancer in Bangladesh, in male it ranks after lung cancer. So far, infection with *Helicobacter pylori* (*H. pylori*) is the strongest recognized risk factor for GC[1]. Chronic infection with the bacterium *H. pylori* causes noncardia gastric carcinoma and low-grade B-cell MALT lymphoma[2]. It was estimated that worldwide 660,000 cases of cancer in the year 2008 were attributable to *H. pylori*, corresponding to 32.4% of the 2 million cancer cases attributable to infectious agents and 5.2% of the 12.7 million total cancer cases that occurred worldwide[3]. The vast majority of the cancers attributable to *H. pylori* (650,000) were noncardia gastric carcinoma[4].

The severity and long-term outcome of this infection is modulated by an increasing list of bacterial, host, and environmental factors, which interplay in a complex manner. Identification of individuals at high risk for GC that may enter a surveillance program and intervention during the precancerous process is the most suitable strategy for decreasing mortality due to this malignancy. The 21st century has brought more attention to infectious agents and chronic active inflammation as primary causes of some cancers. Although the absolute numbers of GC are decreasing in western countries, some studies suggest different patterns in various age groups, with a particular significant increase in premalignant lesions and GC among younger patients[5].

It is also reported that colonization with *H. pylori* is not the sole determinant for the development of GC. Risk modulators are in particular related to lifestyle. The recognition of these risk modulators determines the options for prevention and intervention to decrease the incidence of GC[6]. In Bangladesh some studies are carried out regarding association of *H. pylori* with dyspepsia[7]. But there is no clear sorological evidence found linking to GC. In this study we examined the serological association with GC patients as a case control manner.

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Materials and methods

This case-control study was carried out at the department of Surgical Oncology of National Institute of cancer research and hospital from January 2013 to December 2014. Purposive sampling technique was applied to select cases for this study. All patients with endoscopically and histopathologically proven adenocarcinoma of stomach admitted under surgical Oncology department of NICRH were included in the study. Controls were selected from patients having no cancer on endoscopy, matched to cases by age, sex, socioeconomic status. All cases and controls were evaluated by history, examinations, and investigations. GC cases were classified as cardia or proximal cancer if their location was in gastrooesophageal junction and fundus and as noncardia cancer otherwise, distal cancer if the tumor location was below the mid body or in the antrum. GC was also divided into early and advanced cancer, after pathologic examination following endoscopic or surgical resection. Early gastric cancer (EGC) is defined as a tumor that was confined to the mucosa or submucosa regardless of lymph node involvement, and advanced gastric cancer (AGC) was defined as a tumor that invaded beyond the submucosa. In patients who did not undergo resection due to metastatic GC, tumor stages were determined by endoscopic and computer tomographic findings. GCs were classified histopathologically according to Lauren's system (intestinal, diffuse, and mixed type) and on the grading (well differentiated, moderately differentiated, undifferentiated). Peroperative analysis of most of the cases were performed to see tumor location invasion to adjacent organ, lymph node involvement, ascites, hepatic metastasis, and peritoneal seedlings. Postoperative specimen was sent for histologic examination to see tumor location, stage, grade, and Lauren's type. A blood sample (5 mL without preservative) was obtained from each participant, anti-*H. pylori* IgG was measured using *H. pylori* kit at Bangabandhu Sheikh Mujib Medical University Laboratory. All participants were categorized as seropositive and seronegative for *H. pylori* according to selective cutoff value of IgG. Categorical data were expressed as number and percentage and were compared using the χ^2 test. Multivariate logistic regression was done to analyze the risk for *H. pylori* infection; *P*-value of ≤ 0.05 was considered as significant. For control, adult people above 30 years of age, who attended endoscopical examination for nonspecific abdominal pain were included in this series. Subjects were selected from 3 centers across the country, from Dhaka, Khulna, and Sylhet. None had any feature of malignancy or any pathology by endoscopy.

Results

In this study, 114 GC patients and 520 control subjects were studied. The mean age of the control patients was 46.01 (±13.56) years and that of the case patients was 51.11 (±12.65) years. By category, 81 patients and 309 control patients were males. Additional salt intake and smoking habits were significantly more prevalent in the case group ($P < 0.05$). Case patients were significantly less educated than control patients ($P < 0.05$) (**Table 1**). In the case group 99 patients (86.8%) exhibited seropositivity against *H. pylori* infection, whereas in the control group this percentage was 67.5. This difference of seropositivity was statistically significant (**Table 2**). **Table 3** shows the cross-tabulation of the case patients by the *H. pylori* seropositivity and morphology. No significant association was noted between tumor location, Lauren tumor type, tumor grading, and *H. pylori* seropositivity. Cross-tabulation of the case patients by location, grade, and the type of the carcinoma is presented in **Table 4**. It was found that intestinal type is mostly seen in distal gastric carcinoma while most of the intestinal carcinoma was well to moderately differentiated. Diffuse or mixed type tumors were mainly poorly differentiated. These differences were statistically significant ($P < 0.05$). Multivariate logistic regression analysis of risk for *H. pylori* infection was performed and the result presented in **Table 5**. The odds ratio (OR) of ever smokers was 2.253 higher than nonsmokers. Age below 50 years, male, and additional salt intake were other significant risk factors. **Table 6** depicts the ORs and 95% confidence intervals for the association between *H. pylori* infection and GC by subgroup. It was found that ulceroproliferative type and poorly differentiated carcinoma had higher ORs in contrast to tumor location and type.

Table 1

Baseline characteristics of the patients.

Baseline Characteristics	Category: Control (N = 520 With Percentage)	Case (N = 114 With Percentage)	*P*
Age (mean ± SD) (y)	46.01 (13.56)	51.11 (12.65)	0.654
Male sex	309 (59.4)	81 (71.1)	0.082
Additional salt intake	113 (21.7)	44 (38.6)	0.042
Ever smoking	140 (26.9)	60 (52.6)	0.031
Family income/mo (> 10,000 taka)*	201 (78.7)	87 (76.3)	0.254
SSC or above level education	268 (51.5)	27 (23.7)	0.025

*10,000 taka = 120 USD.
SSC indicates secondary school certificate.

Discussion

Bangladesh is a South Asian developing country, where the rate of *H. pylori* infection is particularly high. Mahalanabis et al[8] in a study of 13C-urea breath test also reported that the prevalence of *H. pylori* was 63% in infants aged 1–3 months, 33% in 10–15-month-old children, and 84% in 6–9 years old. Moreover, the overall *H. pylori* prevalence in other Asian countries including, India (79% by ELISA), Pakistan [84% by polymerase chain reaction (PCR)], and Japan (41% by measuring urinary levels of anti-*H. pylori* antibody) was also reported to be high[9]. In Europe (40%) and the United States (40%), a significantly lower prevalence rate of *H. pylori* was observed[10]. High *H. pylori* infection rates in developing countries compared with the developed world may be the consequence of poor socioeconomic conditions and unhygienic life styles[9].

Table 2

Distribution of *H. pylori* seropositivity among the respondents.

H. pylori Seropositivity	Category: Control (N = 520)	Case (N = 114)	χ^2	*P*
Present	351 (67.5)	99 (86.8)	16.98	< 0.001
Absent	169 (32.5)	15 (13.2)		
Total	520 (100.0)	114 (100.0)		

Percentages are given in the parenthesis.

Table 3

Cross-tabulation of the case patients by the of *H. pylori* seropositivity and morphology (N = 114).

	H. pylori Seropositivity		
Morphology	**Present**	**Absent**	***P***
Tumor location			
Proximal	28 (28.3)	3 (20.0)	0.502
Distal	71 (71.7)	12 (80.0)	
Type			
Intestinal	74 (74.7)	10 (66.7)	0.507
Diffuse/mixed	25 (25.3)	5 (33.3)	
Grading			
Well to moderately differentiated	69 (69.7)	11 (73.3)	0.774
Poorly differentiated	30 (30.3)	4 (26.7)	

Percentages are given in the parenthesis.

We found that among 111 patients, 60 (54.05%) were positive by the CLO test and 54 (48.65%) were positive by PCR. Although PCR is more sensitive and more specific than the CLO test, this study produced unsatisfactory PCR results compared with the results of CLO test[11].

Significantly more patients in the case group (86.8%) were seropositive for *H. pylori* antigen in contrast to the control group (67.5%). This result supports the conclusion by the IARC that infection with *H. pylori* is a risk factor for GC in humans. All of the cases in the present study were in advanced stage. However, in previous analyses, the prevalence of *H. pylori* infection was significantly higher in patients with EGC than in those with AGC[12,13]. Most untreated EGCs are reported to progress to AGC within 4–5 years[14]. The lower frequency of *H. pylori* IgG antibodies in AGC may result from a decrease in antibody titer, due to the development of advanced *H. pylori*-associated atrophic gastritis concomitant with age.

We found no significant association between *H. pylori* seropositivity and tumor location though a strong positive association has been reported between *H. pylori* seropositivity in gastric noncardia adenocarcinoma[13,15,16]. Studies have found a null[13,16] or inversely associated relationship[15] between anti-*H. pylori* seropositivity and gastric cardia cancer. This association shows substantial geographic variation. Most studies in Asian populations have found a positive association between *H. pylori* seropositivity and cardia cancer[12,17], whereas most studies in western populations have found no association or an inverse association[15,18,19]. This discrepancy may have been due to the classification in western studies of some patients with esophageal adenocarcinoma as having gastric cardia cancer[7,15].

Table 4

Cross-tabulation of the case patients by location, grade, and the type of the carcinoma.

	Tumor Types [n (%)]			
Morphology	**Intestinal**	**Diffuse/Mixed**	χ^2	***P***
Tumor location				
Proximal	17 (54.8)	14 (45.2)	6.159	0.013
Distal	65 (78.3)	18 (21.7)		
Grading				
Well to moderately differentiated	71 (87.5)	9 (12.5)	31.398	< 0.001
Poorly differentiated	13 (38.2)	21 (61.8)		

Table 5

Multivariate logistic regression analysis of risk for *H. pylori* Infection.

		95% CI	
Risk for *H. pylori* Infection	**OR**	**Lower**	**Upper**
Age (< 50 y)	1.385	0.624	2.501
Sex (male)	1.401	0.433	4.254
Additional salt intake	1.421	0.771	2.523
Ever smoker	2.312	1.058	4.812
Familial income (< 10,000)	1.151	0.511	2.492
Education (SSC or above)	0.785	0.452	1.617

CI indicates confidence interval; OR, odds ratio; SSC, secondary school certificate.

H. pylori has been reported to be a causal factor in the atrophic gastritis-intestinal metaplasia-intestinal type of GC sequence, hypothesized by Correa[20]. The prevalence of *H. pylori* infection seems to be greater in intestinal type than in diffuse type GCs[21,22]. However, most comprehensive studies have shown that there is no difference in *H. pylori* seroprevalence between these 2 types[13,15,16], a finding consistent with the present study. GC can be classified as differentiated or undifferentiated carcinoma according to Japanese classification[23]. We found that undifferentiated gastric carcinoma had slightly more association with *H. pylori* infection. Although previous studies showed that *H. pylori* infection may be associated with the differentiated, but not the undifferentiated type of GC[24,25]. Moreover, a study in Japan indicated that the ORs were similar (5.8 for differentiated and 5.1 for undifferentiated type[26]). Younger *H. pylori*-infected patients have been found to be at higher relative risk for GC than older patients, a finding consistent with the present study. This can be explained by the lower infection rate in the younger controls, whereas the age-related prevalence of *H. pylori* infection increased significantly with the cohort effect in controls but not in cases[13]. In addition, *H. pylori* prevalence was higher in younger than in older GC patients, which may be due to the spontaneous disappearance of infection caused by increased mucosal atrophy and intestinal metaplasia with advanced age, inhospitable place for *H. pylori* colonization[27–29]. Generally, patients with GC have more severe mucosal atrophy and intestinal metaplasia in the stomach than normal subjects[30]. Another hypothesis is that humoral immune response tends to decrease with age[31], resulting in the underdetection of serum antibodies against *H. pylori*. Meanwhile, earlier reports showed that the prognosis of patients with early onset of GC was poor, with a short survival potential,

Table 6

Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between *H. pylori* infection and gastric cancer by subgroup.

		95% CI	
Factors	**OR**	**Lower**	**Upper**
Ulceroproliferative type	2.121	0.314	11.012
Location (distal)	0.451	0.069	2.531
Lauren's type (diffuse/mixed)	0.445	0.051	3.870
Grade (poorly differentiated)	1.481	0.177	9.521

especially in patients who presented with advanced gastric carcinoma[32,33]. In a few reports, however, the prognosis of patients with early-onset GC who underwent gastrectomy was better than that of older patients[34]. Recent reports have showed no difference in surgical outcomes between older and younger patients with GC[35]. Therefore, age does not seem to be an independent risk factor for GC. Regarding to sex, hormonal difference might be an important factor for prognosis in patients with GC. Several studies found that female sex hormones and their analogs appear to be associated with gastric carcinogenesis and progression, and that pregnancy and delivery may accelerate growth of stomach cancer cells[36,37]. Further studies are needed to evaluate different outcomes between both sexes in young GC patients. A long time study performed in Finland reported that of all GCs that occurred during the 15-year follow-up among elderly men, only 11% appeared in men with healthy stomachs. The risk of stomach cancer is approximately 6 times higher among men with *H. pyloric* infection than among men with healthy stomach mucosa, and the *H. pylori* infection raises the GC risk similarly in the gastric cardia and in other sites of the stomach[38].

Like that of international studies, in Bangladesh *H. pylori* is also found in >80% of GC cases, again it is prevalent in the community also. To date, existing findings indicate that GC is the biological translation of carrying an infectious disease, which is interestingly preventive with anti-*H. pylori* regimen[39]. Therefore, as an inevitable consequence, identification of *H. pylori* colonized in people with high risk of GC is the main direction of the future research. It is postulated that if *H. pylori* can be removed from the population, it has been estimated that ~75% of GC would be eliminated[40]. So it is high time to take an initiative for anti *H. pylori* measures that will help to reduce the number of new cases.

Ethical approval

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Author contribution

K.K.S.: protocol making, study designing, making data collection sheet, taking samples from patients, data compilation, and writing. M.J.K.: selection of the patients, active in surgical intervention, taking samples from the patient, collection of the samples, and data compilation. A.K.M.M.u.B.: selection of the patients, active in surgical intervention, taking samples from the patient, collection of the samples, and data collection. M.S.A.: selection of the patients, active in surgical intervention, taking samples from the patient, collection of the samples. F.R.C.: coordinating the samples for control across the different parts of the country, final data analyzing. M.A.A. and M.A.R.: helping for giving the concepts, endoscopist for patients and controls, and sample collection. M.M.R.: giving the theme, study designing, monitoring all steps like sample collection from patients and control, data analyzing, giving the final shape of the manuscript, responsible for fund collection, and corresponding author. Every author has contributed towards study designing, case selection, data collection, compiling, analysis, and writing.

Conflict of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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