Published in final edited form as:

Helicobacter. 2018 August ; 23(4): e12491. doi:10.1111/hel.12491.

New observations regarding *Helicobacter pylori* and gastric cancer in Mongolia

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Abstract

Background—The incidence and mortality of gastric cancer in Mongolia is among the highest in the world.

Methods—This was a case-control study in which upper gastrointestinal endoscopy, gastric histology, *H. pylori* testing and risk factor questionnaires were obtained. Histological subtypes were determined by Lauren's classification.

Results—We enrolled 45 gastric cancer and 108 non-gastric cancer patients. Gastric cancers were located in upper part of stomach in 53.3%, main gastric body in 37.8% and lower part of stomach in 8.9%. The majority (60%) were diffuse type, followed by intestinal type (36.7%) and indeterminate type (3.3%). *H. pylori* infections were CagA positive in 100% with cancer vs. 81% without cancer ($p = 0.02$). The majority of CagA was non-East Asian type (95% with cancer and 94.1% without cancer). Cancer patients had typically related with excessive use of salt, hot beverages, tobacco smoking and low ingestion of fruits.

Conclusion—The characteristic topography of gastric cancer in Mongolia being in the gastric corpus differed from East Asian countries and was more similar to western countries. The risk factors for gastric cancer in Mongolia were similar to other high risk areas (i.e., *H. pylori* infection, excessive use of salt, tobacco smoking and low ingestion of fruits).

Keywords

Gastric cancer; *Helicobacter pylori*; environmental risk factors; Mongolia

1: INTRODUCTION

Gastric cancer is the third leading cause of cancer-related deaths worldwide with the highest incidence in East Asian countries. The age standardized rate (ASR) per 100,000 population of gastric cancer incidence are 41.8 in Korea, 32.5 in Mongolia and 29.9 in Japan for both sexes (1). Gastric cancer is divided by anatomical location into cardia area cancer (proximal part) and non-cardia cancer (arising from the remainder of the stomach) (2). *Helicobacter pylori* infection is the major cause of non-cardia cancer and cardia cancer in Asia (3, 4) whereas in studies from some western countries cardia cancer is associated with obesity, gastroesophageal reflux and tobacco smoking (5, 6).

The incidence of proximal to distal gastric cancer varies geographically (7) with the majority of cancer from East Asian countries such as Japan, Korea and China arising from the distal part of stomach (8, 9). In these regions most *H. pylori* contain CagA of the East Asian type which has been suggested to be especially virulent (10, 11). Globally there has been a trend for gastric cancer to decrease in part related to the fall in *H. pylori* prevalence as well as changes in food preservation and year around availability of fresh fruits and vegetables (12, 13). Proximal cancer which overlaps with esophageal adenocarcinoma has been noted to have increased in western (14–18), and some East Asian countries (19, 20) are typically associated with non-atrophic gastric mucosa and absence of *H. pylori*.

Mongolia is located in East-Central Asia between Russia and China. According to a nationwide survey conducted in accordance with international standards by World Health Organization for non-communicable disease risk factors, the Mongolian diet contains a high proportion of animal fat and red meat with high salt usage with lower amounts of vegetables and fruit. On average their body mass index is relatively high (21–23). A previous study among 208 non-gastric cancer dyspeptic non-gastric cancer patients showed approximately 70% were infected with *H. pylori* (24). The present study was designed to identify cancer risk factors in Mongolia (25) to assist in developing a screening strategy for individuals at increased risk.

2: METHODS

2.1: Study population and sampling

We conducted a case control study among gastric cancer and non-gastric cancer patients, from November 2014 to August 2016. Experienced Japanese and Mongolian endoscopists certificated by Japanese and Mongolian society for gastroenterology/endoscopy, respectively

performed the endoscopic examinations. The gastric cancer group consisted of consecutive consenting gastric cancer patients recruited from endoscopy at the Mongolian National Cancer Center Hospital (Ulaanbaatar; October 2015 to August 2016) which admits patients from all nationwide provinces.

Subjects with non-gastric cancer dyspepsia were recruited from different areas in Mongolia: Uvs Province (Western part of Mongolia), Khuvsgul Province (Northern), Umnugovi Province (Southern) and Khentii Province (Eastern) (Figure 1). We enrolled dyspeptic subjects more than 40 years old with a male to female ratio of 2 based on the fact that the risk of gastric cancer for males is generally twice that for females and because the age at which gastric cancer risk begins to rise exponentially varies among regions, but it is typically at over 40 years old (1, 26, 27).

The desired sample size was calculated according to the Fleiss statistical method (28) using the following conditions: two side confidence level of 95%, detecting power of percentage of 80%, ratio of control to case of 3, hypothetical proportion of controls with exposure of 40% and hypothetical proportion of cases with exposure of 70%. The optimum sample size was calculated as 173 (36 for cases and 108 for controls). To control for false positive diagnoses we increased the sample size by 25% for cases. The control group consisted of 27 individuals from each province (18 men and 9 women).

The gastric cancer group included gastric cancer patients with no history of usage of antibiotic or acid inhibitor use within one month prior to the start of the study. Inclusion criteria for the control group included upper digestive tract dyspeptic symptoms and age 40 years old or above. History of gastrectomy, endoscopic mucosal dissection or previous history of *H. pylori* eradication therapy was exclusion criteria. If a gastric or duodenal ulcer was found at endoscopy, the subject was excluded. Those with gastric cancer were included in the “cancer group”.

Blood samples from all participants were collected and serum was separated on the same day as endoscopy. During endoscopic examination at least three biopsy specimens were taken from the antrum. One was used for rapid urease test (Mon-HP, developed at the Mongolian National University of Medical sciences, Ulaanbaatar, Mongolia) and one for culture of *H. pylori* and remaining were used for histology. One biopsy specimen for histological examination was taken from the greater curvature of the corpus. If gastric cancer was suspected one or two more specimens were taken for histological examination. All patients were carefully examined by experienced endoscopists.

In provinces other than Ulaanbaatar, serum and biopsy specimens for culture were frozen at -20°C temporarily, transported to Ulaanbaatar on dry ice where they were kept at -80°C . The samples were then sent to Oita University Faculty of Medicine (Yufu, Japan) on dry ice and were kept at -80°C until analyzed.

Written informed consent was obtained from all participants, and the protocol was approved by Mongolian Ethics Committee at Ministry of health and by Oita University Faculty of Medicine. The questionnaire was filled out by the clinicians before the endoscopic examination.

2.2: Endoscopic criteria

For non-malignant endoscopic mucosal details the Los Angeles classification (erosive esophagitis: LA grade A-D and non-erosive esophagitis) was used to define esophagitis (29). Gastric mucosal atrophy was evaluated using the Kimura-Takemoto's classification (30). By this classification atrophy was classified as close type (denoted mild atrophy which is limited in the antrum and lesser curvature of the proximal corpus) and open type (denoted advanced atrophy which is more extended into corpus and cardia). The location of gastric cancers was subdivided into upper, middle and lower part of stomach according to Japanese classification of gastric carcinoma (31). If the cancer was located two regions (e.g., upper and middle stomach) the predominant area involved was used as the location. Borrmann's classification (32) was used for advanced gastric cancer and Japanese endoscopic criteria was used for early stage gastric cancer (33).

2.3: Histological diagnosis of gastric cancer and *H. pylori* infection

All gastric biopsy specimens were fixed in 10% buffered formalin and embedded in paraffin. Serial sections were stained with hematoxylin and eosin and with the May-Giemsa stain. For suspected gastric cancer cases the stained slides were described using Lauren's classification and the Japanese classification of gastric carcinoma (34, 35). For non-malignant mucosal background the acute inflammation (polymorphonuclear neutrophil infiltration), chronic inflammation (mononuclear cell infiltration), atrophy, intestinal metaplasia (IM), and bacterial density were classified into four grades, according to the updated Sydney system: 0, 'normal'; 1, 'mild'; 2, 'moderate'; and 3, 'marked' (36). Samples with a grade of 1 or higher were considered as positive status. To minimize the potential bias between studies, an experienced pathologist (TU) performed the experiments, who also performed experiments for Nepal, Bhutan, Bangladesh, Myanmar, Thailand, Vietnam, Indonesia and Dominican Republic (24, 37–42).

2.4: Determination of *H. pylori* infection by immunohistochemistry

For *H. pylori* diagnosis, culture, histology confirmed by immunohistochemistry (IHC), rapid urease test and serological tests were used. *H. pylori* culture was performed as previously described (43). IHC for anti-*H. pylori* antibody (Dako, Glostrup, Denmark), polyclonal anti-CagA antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) and anti-East Asian specific antibody was performed as previously described (44). The serologic test used commercial ELISA kits for anti-*H. pylori* IgG (Eiken Co., Ltd, Tokyo, Japan) and serum CagA antibody (Genesis, Diagnostics, USA). Detailed *H. pylori* infection criteria are described in Suppl. Figure 1.

2.5: Modifiable and non-modifiable risk factors

Age, gender and ethnic background status were used for non-modifiable risk factors. The body mass index (BMI), diet and unhealthy habits were used for modifiable risk factors. Physicians completed risk factor questionnaires before the endoscopic examination. Body mass index (BMI) was categorized as follows; underweight: under 18.5 kg/m², normal weight: BMI; 18.5 to 24.9, overweight: 25 to 29, obese: over 30. For diet-habits questionnaire, lower usages of vegetable or fruits (yes status: less than 100–200 gram per

day) and routinely drink hot beverages (with visible steam) were included. Previous nationwide study validated questionnaires evaluated excessive salt usage using 24 hour urine collection samples which showed urine salt levels were highest among daily salty tea drinkers, confirming the accuracy of questionnaire method (45). Therefore to identify excessive use of salt, we used the questionnaire method to screen for those who consumed salty tea every day. Unhealthy habits were defined as; tobacco use (yes status: daily smokers), alcohol (yes status: excessive amount of standard drink [350 mL glass of beer, 150 mL glass of 12% wine, or 44 mL glass of spirit] per daily).

2.6: Statistical analysis

Statistical significance of the qualitative differences was calculated using the chi-square and Fisher's exact test. Mann-Whitney U test was used for continues variables. Etiological risk factors of gastric cancer were calculated by backward logistic regression analysis. By univariate analysis all factors with p values less than 0.25 were involved in multivariate analysis. All statistical analyses were performed using the IBM SPSS Version 22.0 (IBM Corp. Armonk, NY, USA) software.

3: RESULT

3.1: Characteristics of gastric cancer and its background

Experienced endoscopists collected gastric mucosal specimens from consecutive patients in Uvs Province (July 14–21, 2015), Khuvsgul Province (July 19–25, 2015), Umnugovi Province (August 4–8, 2016) and Khentii Province (August 9–12, 2016). We enrolled 108 control cases (27 [18 men and 9 women] from each province) and 63 suspected gastric cancer patients: 50 from the National Cancer Center and 5 from the provinces during survey on dyspeptic patients (2 from Uvs Province, 2 from Khuvsgul Province and 1 from Umnugovi Province). Among 55 suspected gastric cancer cases, 45 were confirmed as gastric cancer by histology. We excluded 3 with benign ulcers and 7 with advanced gastric cancer involving lower esophagus. In total, 108 control gastritis group and 45 gastric cancer group were included in this study.

The majority of gastric cancers were advanced stage (84.4% [38/45]). According to Bormann's classification for advanced gastric cancer, most cases were type III (60.5% [23/38]) followed by type IV (21.1% [8/38]) and type II (18.4% [7/38]). The remaining cases were belonged early stage gastric cancer (14.8% [8/54]). Among them IIa+IIc (42.8% [3/7]), IIc (28.6% [2/7]), IIa (14.3% [1/7]) and IIb (14.3% [1/7]) stage gastric cancer were diagnosed. Among gastric cancer patients, 53.3% (24/45) was located in upper part of stomach, 37.8% (17/45) was located in middle part of corpus and 8.9% (4/45) was in the antrum (lower part of stomach).

Demography, endoscopy and prevalence of risk factors are shown in Table1. The gastric cancer group ranged in age from 27 to 78 years old; 5 gastric cancer patients were less than 40 years old. Using Kimura-Takemoto's endoscopic classification open-type atrophy was significantly more frequent (33.3%) in gastric cancer patients than non-cancer controls (6.5%) ($p = 0.02$). For environmental risk factors; daily drinking salty tea ($p = 0.0001$),

tobacco smoking ($p = 0.002$), drinking hot beverages ($p = 0.001$) and eating a low amount of fruit ($p = 0.005$) were significantly more common in gastric cancer patients than controls (Table 1). Multivariate analyses for etiological risk factors showed that salty tea, tobacco smoking, hot beverages and low usage of fruits were remained to increase risk for gastric cancer (Odds ratio [95% confidence interval]; 3.3 [1.4–7.8], 3.2 [1.4–7.1], 3.7 [1.6–8.8], and 2.6 [1.1–6.1], respectively).

3.2: *H. pylori* infection and CagA status

The prevalence of current/past *H. pylori* infection and CagA status for control and gastric cancer subjects are shown in Table 2. *H. pylori* prevalence was high and was not significantly different among groups. All gastric cancer patients were infected with CagA-positive strains as were the majority of controls (81.2%) ($p = 0.01$). The majority of CagA-positive cases were non-East-Asian-type in control (95%) and gastric cancer group (94.1%).

By *H. pylori* infection status, the proportion of histological subtype of gastric cancer is shown in Figure 2. Middle gastric body cancers had higher proportion of diffuse type cancer than upper and lower part of stomach cancer.

3.3: Histological background in gastric cancer and gastritis group

Histological analyses were limited to the antrum because only one corpus biopsy specimen was allowed. Atrophy and IM scores were significantly higher in gastric cancer than in control group, which was consistent with our endoscopic findings (Kimura-Takemoto's endoscopic classification) and with gastric cancer being a manifestation of advanced and extensive atrophy. Atrophy and IM scores were higher in lower part of gastric cancer than middle and upper part of gastric cancer.

4: DISCUSSION

Mongolia has one of the highest mortalities from gastric cancer in the world (1). Here, we characterized features of gastric cancer and its risk factors among the Mongolian population. *H. pylori* infection is recognized as playing a major etiologic role in gastric cancer pathogenesis with atrophic gastritis and development of metaplastic gastric epithelium considered the most important recognizable risk factors (11, 46). In western countries cancer in the distal-esophagus and gastric cardia is most often seen in *H. pylori* negative patients and in the United States more than 20% of gastric cancers are now located in the cardia (47). It has been reported that *H. pylori* seropositivity was present in 58% of cardia gastric cancer and 68–85% in non-cardia gastric cancers (48). In the East Asian countries such as Japan, only 4.1% of gastric cancer are located in the cardia with an *H. pylori* positivity of 75.6% in cardia gastric cancer and 83% in non-cardia gastric cancer (49). A recent Japanese multicenter collaborative study showed that cardia gastric cancer located below the esophageal-gastric junction (EGJ) was typically associated with *H. pylori* infection and gastric atrophy (50). They confirmed that 61% of tumors with endoscopic gastric mucosal atrophy were located below the EGJ line (i.e., in the stomach) whereas 81% of EGJ adenocarcinomas not associated with endoscopic gastric mucosal atrophy were located above the EGJ line (i.e., in the esophagus) and were associated with GERD (50). The

distribution of gastric cancers within the Mongolian stomach was more typical of that seen in western populations than is seen in Japan. In this study gastric cancers in Mongolia were often diffuse type which was significantly more common in the middle gastric corpus than in the antrum or upper part of the corpus (Figure 2). Intestinal type gastric cancer was predominately located in the lower (antrum) part of stomach (Figure 2). The ratio of diffuse type to intestinal type gastric cancer (1.5 [29/19]) was higher than some East Asian (0.5–1.3) and Western (0.43–0.74) countries (51–55). The sample in this study was a convenience sample and additional larger studies will be needed to confirm the characteristics of gastric cancer in Mongolia.

Previously, the East-Asian-type CagA was considered to an especially virulent marker (56, 57) and we hypothesized that most *H. pylori* in Mongolia would contain East-Asian-type CagA. However the CagA subtypes in Mongolia were non-East-Asian-type casting doubt on the notion that the high risk of gastric cancer in East Asia reflects the presence of an especially virulent type of CagA. Nonetheless, strains possessing CagA are associated with an increased inflammatory response such that the risk of cancer is doubled (58, 59). In addition, recent studies evaluating gastric histology in Japan over 4 decades have shown a marked decline in the prevalence of atrophy among those with *H. pylori* infection coincident with a change in diet and smoking (60). This study suggest that there is likely little if any difference in virulence between East Asian and western type CagA's and that diet and environmental factors play the major role in determining the relative cancer risk in an *H. pylori* infected population. Noteworthy, these environmental factors such as excessive amount of salt, hot beverages, tobacco smoking and eating less fresh fruits were significantly high in gastric cancer group than control group (Table 1).

In our study 44.4% of gastric cancer patients were *H. pylori* negative by histology, culture and serology tests (Table 2). Although it is likely that *H. pylori* had disappeared long ago as a consequence of development of atrophic gastric mucosa, it is possible that atrophy was caused by another cause such as EBV. This study was a pilot study involving a convenience sample and subsequent studies including a wider age range and random sampling will be needed along with gastric mucosal mapping to determine if factors other than *H. pylori* infection are involved in gastric cancer in Mongolia (61, 62). Our study confirmed that environmental risk factors such as excessive amount of salt usage, tobacco smoking, drinking hot beverages and less usages of fresh fruit was significantly higher in gastric cancer patients than controls (Table 1). Other factors such as microbial dysbiosis still remain to be examined. Finally, we suggest that in addition to *H. pylori* eradication, managing modifiable risk factors might helpful for decreasing gastric cancer incidence and mortality rate. The high incidence of gastric cancer suggests that many Mongolians are at high risk a program of endoscopic surveillance of high risk patients will likely need to be established.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding

Helicobacter. Author manuscript; available in PMC 2019 August 01.

This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (26640114, 15H02657 and 16H05191) (Y.Y.), the Special Coordination Funds for Promoting Science and Technology from the MEXT of Japan (Y.Y.), and National Institutes of Health Grants DK62813 (Y.Y.). B.G and DA are doctoral students supported by the Japanese Government (Monbukagakusho: MEXT) Scholarship Program for 2014 and 2016.

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Figure 1. Sampling population map

Gray colored area showed our chosen places for the survey that Ulaanbaatar is the capital city, Uvs (western part of Mongolia), Khuvsgul (northern part), Umnugovi (southern part) and Khentii (eastern part). Black circles showed the city names that we collected samples.

Figure 2. Gastric cancer subtypes and *H. pylori* infection

The case numbers and percentages of histological subtypes of gastric cancer are shown according to anatomical location of gastric cancer based on *H. pylori* infection status.

Table 1

Demography and background of gastric cancer

Parameters	Control	Gastric cancer	P value	Gastric cancer location		
				Lower	Middle	Upper
Case number	n=108	n=45		n=4	n=17	n=24
Age range	40–79	27–78		35–67	35–71	27–71
Mean age with SD	52.8±8.7	54±11.8	-	46.8±15	54±10.3	55±12.7
Demography						
Male	67%	80%	-	50.0%	88.2%	79.2%
Female	33%	20%	-	50.0%	11.8%	20.8%
Major ethnic	75.0%	84.4%	-	66.7%	75.0%	82.4%
Minor ethnic	25.0%	15.6%	-	33.3%	25.0%	17.6%
Gastritis	73.1%	46.7%	0.02	25.0%	64.7%	37.5%
Endoscopy						
Close type atrophy	20.4%	20.0%		50.0%	23.5%	37.5%
Open type atrophy	6.5%	33.3%		25.0%	11.8%	25%
Bile reflux (yes)	7.4%	11.1%		25.0%	17.6%	4.2%
Salty tea (yes)	45.0%	77.3%	0.0001	100.0%	70.6%	78.3%
Hot beverages (yes)	46.3%	77.3%	0.0001	75.0%	64.7%	37.5%
Alcohol drinking (yes)	38.0%	51.1%	-	100%	62.5%	41.2%
Environmental risk factors						
Tobacco smoking (yes)	27.8%	54.5%	0.002	33.3%	64.7%	50.0%
Eat fresh fruit (yes)	48.0%	23.8%	0.005	75%	11.8%	23.8%
Eat vegetables (yes)	89.8%	83.3%	-	100.0%	82.4%	81%
Overweight (yes)	53.7%	31.3%	-	25.0%	35.3%	29.2%

p value was calculated by chi-square test

Table 2

Helicobacter pylori

infection status

Parameters	Control	Gastric cancer	P value	Gastric cancer location		
				Lower	Middle	Upper
Case number	n=108	n=45		n=4	n=17	n=24
<i>H. pylori</i> infection status						
Negative	25.9%	41.7%	-	50.0%	50.0%	29.4%
Positive	74.1%	57.4%		50.0%	41.2%	54.2%
Overall positive status ^a						
Past	10.0%	12.0%	-	0.0%	0.0%	18.7%
Current	90.0%	88.0%		100%	100%	81.3%
CagA status by IHC ^b			0.01			
CagA(-)	18.8%	0.0%		0.0%	0.0%	0.0%
CagA(+)	81.2%	100%		100%	100%	100%
CagA subtyping by IHC ^c						
CagA(+)	95.0%	94.1%	-	100%	100%	90.9%
CagA(+) East Asian-type	5.0%	5.9%		0.0%	0.0%	9.1%

^a -Overall *H. pylori* positive patients: Control n=80 and GC n=25 (lower n=2, middle n=7, upper n=16)^b -Overall *H. pylori* positive patients: Control n=72 and GC n=17 (lower n=2, middle n=4, upper n=11)^c -Overall *H. pylori* positive patients: Control n=56 and GC n=17 (lower n=2, middle n=4, upper n=11)^d *p* value calculated by chi-square test