ORIGINAL ARTICLE
A PROSPECTIVE EVALUATION OF 200
UPPER ENDOSCOPIES PERFORMED
IN ALASKA NATIVE PERSONS

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Received 16 August 2006; Accepted 2 February 2007

ABSTRACT

Objectives. To characterize the nature and prevalence of disease in Alaska Native patients referred for evaluation of upper gastrointestinal signs and symptoms.

Study Design. Cross-sectional.

Methods. Two hundred consecutive Alaska Native patients referred to a statewide tertiary center were prospectively evaluated. A standardized data collection form documenting EGD findings was utilized. Routine biopsies of the antrum and fundus were taken on all patients. Additional tissue was obtained from any areas of clinical concern.

Results. Among 200 patients who underwent EGD during the study period, 130 (65%) tested H. pylori-positive on histology. Among 173 patients with histologic evidence of gastritis, 114 (66%) tested H. pylori-positive on histology. Chronic gastritis (87%), gastric ulcer (GU 12%), duodenal ulcer (DU 3%) and gastric cancer (2%) were the predominant findings. The GU:DU ratio was 4:1, the inverse of that reported in the general U.S. population.

Conclusions. Alaska Native patients referred for upper endoscopy have a high rate of H. pylori infection with predominantly gastric manifestations of disease and a GU:DU ratio, which is the inverse of what is typically seen in the U.S. and other developed countries. The high prevalence of H. pylori in Alaska Native patients resembles prevalence patterns reported from developing countries and may be linked to a rate of gastric cancer that is over three times that found in the U.S. population at large. (Int J Circumpolar Health 2007; 66(2) 144-152)

Keywords: ulcer, Helicobacter pylori, gastritis, endoscopy, gastric cancer, Alaska Native
INTRODUCTION

The prevalence of diseases of the upper gastrointestinal (GI) tract varies among different populations. A variety of dietary, environmental, infectious and genetic factors have been implicated in these differences (1). Clinicians working in Alaska have noted that Alaska Native persons (of predominantly Eskimo, Indian or Aleut descent) appear to have high rates of gastric cancer, gastric ulcer and gastritis compared with the Caucasian population in Alaska and the rest of the U.S. (2,3). A high seroprevalence of antibodies to *H. pylori* (75%) has been shown in this population. In addition, elevated rates of gastric cancer, compared with the Caucasian population in Alaska and the rest of the U.S., have been demonstrated (4,5). Other than a single retrospective review 30 years ago, little has been published on upper gastrointestinal disease in this unique group of patients (2). This is a prospective review of 200 consecutive esophagogastroduodenoscopies (EGDs) performed on Alaska Native persons referred with signs, symptoms or a history of upper gastrointestinal disease.

MATERIAL AND METHODS

The Alaska Native Medical Center (ANMC) located in Anchorage, Alaska, serves as a referral hospital for approximately 95,000 Alaska Native people living in state, about 23,000 of those residing in the Anchorage area. ANMC serves both groups, and surgeons and internists participating in this study functioned as consultants for all patients being considered for endoscopy. Patients 18 years of age or older, referred to the surgery or internal medicine staff for upper gastrointestinal symptoms or for follow-up of previous abnormal EGD findings (i.e., Barrett’s esophagus), comprised the study population. We found no differences in overall findings between persons on first and follow-up EGD and, consequently, results are not reported here. The clinical decision to perform an EGD was made by the consulting physician. Procedures were performed by 7 different examiners. Two hundred consecutive EGDs, performed between May and November of 1993, were analyzed. Endoscopic findings were documented concurrently using a standardized form describing location of lesions and grading of inflammatory changes. Presence of gastritis was evaluated at the following sites: antrum, body, fundus and pre-pylorus. Tissue specimens were obtained from the antrum and fundus on all patients and additional biopsies were taken from any areas of clinical concern. Specimens were reviewed by 3 staff pathologists using both hematoxylin and eosin (H&E) and silver staining techniques to determine the presence of *H. pylori*. Serologic and urea breath testing were not performed. The Alaska Area Institutional Review Board determined that the study was exempt because no additional tests were performed on clinical samples and all patient identifiers were removed prior to data analysis. Slides from approximately 10% of patients were sent for external review to pathologists outside ANMC who had expertise in *H. pylori* histology (6). There was a greater than 95% concordance among the ANMC pathologists and similar agreement with the outside reviewers.
Statistical analysis
Statistical analyses were conducted using SAS (version 6.12, SAS Institute, Cary, NC). Categorical variables and continuous variables were compared between groups by use of the chi-square and Wilcoxon two-sample test, respectively. P-values were 2-tailed, and values less than .05 were considered statistically significant. P-values are exact for tests conducted with small sample sizes.

RESULTS

Patient characteristics and reasons for referral
Among the 200 Alaska Native patients, 90 (45%) were female; the mean age of persons undergoing EGD was 54 years (range 18 to 85 years). Almost half of the patients (47%) were residents of Anchorage (Table I). Twenty-one persons (11%) had a previous history of

Table I. Characteristics of the 200 Alaska Native patients that underwent endoscopy, 1993. Previous medical conditions determined by medical chart review.

| Characteristic                          | n (%)      |
|----------------------------------------|------------|
| Age category (years)                   |            |
| < 40                                   | 44 (22%)   |
| 40 - < 50                              | 36 (18%)   |
| 50 - < 65                              | 71 (36%)   |
| ≥ 65                                   | 49 (24%)   |
| Female                                 |            |
| Southcentral (Anchorage)               | 94 (47%)   |
| Western                                | 22 (11%)   |
| Southwestern                           | 19 (10%)   |
| Northern                               | 19 (10%)   |
| Northwestern                           | 16 (8%)    |
| Other                                  | 29 (14%)   |
| Current tobacco use (within last 2 weeks) |          |
| Current alcohol use (within last 2 weeks) |          |
| Previous gastric ulcer                 | 41 (20%)   |
| Previous duodenal ulcer                | 14 (7%)    |
| Previous esophageal ulcer              | 3 (1%)     |
| Previous gastritis                     | 28 (14%)   |
| Previous Barrett’s Esophagus           | 12 (6%)    |
| Previous gastric surgery               | 12 (6%)    |

Table II. Reasons for referral.

| Number of Patients (% of total) | Symptoms                                      |
|---------------------------------|-----------------------------------------------|
| 1 (1%)                          | Esophageal stricture                           |
| 39 (19%)                        | UGI bleed                                      |
| 28 (14%)                        | Reflux symptoms                                |
| 90 (45%)                        | Abdominal pain                                 |
| 4 (2%)                          | Anemia and heme + stool                        |
| 10 (5%)                         | Anemia only                                    |
| 5 (2%)                          | Heme + stool only                              |
| 9 (5%)                          | Other (unspecified in database)                |
| 14 (7%)                         | Asymptomatic (follow-up Barrett’s esophagus)   |
| 200 Total                       |                                               |
H. pylori infection (diagnosed by endoscopic evaluation), while 58 persons (29%) had a history of ulcer disease. Anchorage residents were older than rural residents (median age = 59 versus 47 years); however, we found no differences between these two groups in terms of referral symptoms or medical history (history of ulcers, gastritis or previous H. pylori infection) before and after adjustment for age. Reasons for referral are described in Table II.

**Endoscopic findings**

Gastritis, the most common endoscopic finding, was noted in 140 (70%) patients examined and was characterized as diffuse process. The number of patients with inflammation in the distal stomach (prepyloric and antrum and region) and proximal stomach (body and fundus) was similar (Table III).

Overall, 29 (14.5%) patients undergoing endoscopy had ulcers; 6 (20.7%) were duodenal; and 23 (79.3%) were gastric. There were 3.8 times as many patients with gastric ulcers as with duodenal ulcers. In addition, 3 patients had esophageal ulcers. No differences were found between those persons with and without ulcers (all types) in terms of gender, age at endoscopy or region of residence.

Among the 4 persons with a gastric malignancy, 3 (75%) had gastritis, 1 also had a duodenal ulcer. One of the malignancies was in a gastric ulcer; the other 3 patients had gastric masses. No cases of esophageal or duodenal malignancy were detected and no esophageal varices were reported. Only 14% of patients had an exam characterized as completely normal by the examiner (Table III).

**Pathologic findings**

Among the 173 (87%) patients whose biopsy tissue demonstrated histological evidence of gastritis, 114 (66%) showed evidence of infection with H. pylori (Table IV). Fifty-nine (34%) demonstrated histological evidence of chronic gastritis but no evidence of infection with H. pylori. Among these 59 patients, 41% (n = 24) had other potential contributing factors to their gastritis (2 NSAIDs use, 11 ETOH use, and 11 history of H. pylori infection) which did not differ from the 39% (44/114) in persons with active H. pylori infection. Four of 6 (67%) persons with duodenal ulcers were positive for H. pylori by pathology along with all (3 of 3) persons with an esophageal ulcer and 57% (13 of 23) of persons with gastric ulcers. There were 12 persons with a gastric or duodenal ulcer with no H. pylori infection. Of these 12, 2 were using NSAIDs and 2 were consuming ETOH. Among 4 patients diagnosed with a gastric malignancy (3 invasive and 1 in-situ carcinoma), 2 (50%) were H. pylori-positive by histology and all had findings of chronic gastritis. Four additional patients had dysplasia or intestinal metaplasia on gastric biopsy and 1 of these also had evidence of infection with H. pylori.

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**Table III.** Endoscopic findings on 200 consecutive Alaska Native patients, 1993.

| Findings        | n (%)       |
|------------------|-------------|
| (Total = 200)*   |             |
| Esophagitis      | 34 (17%)    |
| Gastritis (total)| 140 (70%)   |
| Prepyloric       | 35 (18%)    |
| Antral           | 96 (48%)    |
| Body             | 61 (31%)    |
| Fundus           | 78 (39%)    |
| Duodenitis       | 23 (12%)    |
| Esophageal ulcer | 3 (2%)      |
| Duodenal ulcer   | 6 (3%)      |
| Gastric ulcer    | 23 (12%)    |
| Gastric tumor    | 4 (2%)      |
| Normal exam      | 28 (14%)    |

*Total exceeds 200 as some patients had more than one finding.
Endoscopic Evaluation of 200 Alaska Natives

\textit{H. pylori} infection

**Histologic evaluation**

Overall, 65\% (n = 130) of persons undergoing EGD were positive for \textit{H. pylori} by pathology. There were no differences between \textit{H. pylori}-negative and \textit{H. pylori}-positive persons in terms of sex or age. Among persons residing outside of the Southcentral region (which includes the Anchorage metropolitan area), residents of Northwestern Alaska had the highest prevalence of \textit{H. pylori} by pathology at 94\% (15/16, \(p < 0.01\) compared with others) followed by 74\% (14/19) of persons from Northern Alaska, 73\% (16/22) from Western Alaska, and 58\% (11/19) from Southwestern Alaska. Sixty-five percent (61/94) of participants residing in the Southcentral region were positive for \textit{H. pylori} by pathology.

\textit{H. pylori} positivity was not associated with the pathological findings of gastritis or duodenitis; however, persons with esophagitis were more likely to be positive (88\%, 15/17) than those without esophagitis (63\%, 115/183, \(p = 0.04\)). Four of 5 persons with Barrett's esophagus were positive for \textit{H. pylori}. Additionally, 2 of 4 participants with gastric dysplasia or intestinal metaplasia were positive for \textit{H. pylori}.

| Table IV. Pathology results among Alaska Native Patients, 1993. |
|---------------------------------|------------------|------------------|
| Finding                        | Number of patients | Helicobacter positive | Percentage \(H. pylori\) positive |
|--------------------------------|-------------------|----------------------|----------------------------------|
| Gastritis                      | 173               | 114                  | 66\%                             |
| Esophagitis                    | 17                | 15                   | 88\%                             |
| Duodenitis                     | 25                | 16                   | 64\%                             |
| Gastric malignancy             | 4                 | 2                    | 50\%                             |
| Gastric dysplasia or intestinal metaplasia | 4 | 1 | 25\% |
| Barrett's esophagus            | 5                 | 4                    | 80\%                             |
| Normal                         | 6                 | 0                    | 0\%                              |

| Table V. \textit{H. pylori} status according to demographics and pathology findings among Alaska Native Patients, 1993. |
|------------------------------------------|------------------|------------------|
| Characteristic                          | HP positives \(n = 130\) | HP negatives \(n = 70\) |
| Mean age                                 | 53.7 years       | 51.4 years       |
| % Female                                 | 56 (43\%)        | 34 (49\%)        |
| Gastritis                                | 114 (88\%)       | 59 (84\%)        |
| Esophagitis                              | 15 (12\%)        | 2 (3\%)          |
| Duodenitis                               | 16 (12\%)        | 9 (13\%)         |
| Gastric malignancy                       | 2 (2\%)          | 2 (3\%)          |
| Gastric dysplasia or intestinal metaplasia | 1 (1\%)        | 3 (4\%)          |
| Barrett's esophagus                      | 4 (3\%)          | 1 (1\%)          |
| Ulcer                                    | 20 (15\%)        | 12 (17\%)        |
| Duodenal                                 | 4 (3\%)          | 2 (3\%)          |
| Esophagalal                              | 3 (2\%)          | 0 (0\%)          |
| Gastric                                  | 13 (10\%)        | 10 (14\%)        |
| Normal pathology                         | 0 (0\%)          | 6 (9\%)          |

\(^{a} \quad p\text{-value} < 0.05\).
cancer and 1 of 4 participants with atypical pathology were positive for \textit{H. pylori}. The 6 patients with normal pathology were all \textit{H. pylori} negative (Table IV).

\textbf{EGD evaluation}

Persons with duodenitis or esophagitis by EGD evaluation were more likely to be infected with \textit{H. pylori} (79\%, 44/56) compared with those without either of these two conditions (60\%, 86/144, \(p = 0.01\)). Sixty-nine percent (96/140) of persons with gastritis noted anywhere by the endoscopist were positive for \textit{H. pylori}, which did not differ significantly from those without gastritis (57\% [34/60], \(p = 0.11\)). However, those with gastritis found in the pre-pylorus were more likely to be infected with \textit{H. pylori} (80\%, 28/35) than all others (62\%, 102/165, \(p = 0.04\)). When considering location of inflammation, including the esophagus, duodenum and stomach, those with inflammation in the pre-pylorus were most likely to carry \textit{H. pylori} (80\%, 28/35), followed by those with inflammation anywhere else (67\%, 84/125), followed by those with no inflammation (45\%, 18/40, \(p < 0.01\)). In the 28 patients with a normal appearance to the gastric lining, 43\% were positive for \textit{H. pylori} and 71\% showed evidence of chronic gastritis on histology.

Seven persons had received treatment for \textit{H. pylori} within the previous 12 months (43\%, 3/7 positive for \textit{H. pylori}) while 24 persons had taken a proton pump inhibitor (25\%, 6/24 positive for \textit{H. pylori}). When persons who had taken a proton pump inhibitor or received treatment for \textit{H. pylori} within the previous 12 months were excluded, 72\% (121/169) of persons were positive for \textit{H. pylori}. Associations between \textit{H. pylori} positivity and gender, age, region of residence and EGD findings are similar within this subset to the preceding results for the entire group.

\textbf{DISCUSSION}

The pattern of upper gastrointestinal pathology among Alaska Native persons differs from that of other U.S. populations, but it is similar to some other populations around the world that have high rates of \textit{H. pylori} infection (7). Thompson and Ackerstein in 1975 reported that the ratio of duodenal:gastric ulcers in Alaska Native persons seemed to be decreased from the expected 3-4:1 to approximately 1.2:1 (2). The Inuit population in Greenland has also been noted to have an inverse ratio of DU:GU with approximately 4 times the number of ulcers in gastric locations compared to the duodenum. In the Greenland report, this inverse ratio was thought to be from a decrease in the number of duodenal ulcers rather than an increase in the number of gastric ulcers when compared with non-native Greenlanders (8). Sample sizes limited our power to detect differences in demographic or clinical characteristics when comparing persons with and without ulcers.

The high prevalence of chronic gastritis in the majority of our patients undergoing EGD is similar to the findings of Yip et al. demonstrating GI blood loss in Alaska Native persons. In their study, they demonstrated a high prevalence (96\%) of chronic gastritis in Alaska Native persons who were
undergoing upper and lower endoscopy to determine the source of GI blood loss. They postulated that chronic inflammation of the gastric mucosa may be responsible for the increased GI blood loss and iron deficiency that has been long noted in Alaska Native persons (9). Our cohort was not specifically evaluated for GI blood loss or anemia, but our endoscopic findings were similar.

The gastric predominant findings in our sample and the documented higher rates of gastric cancer are consistent with the speculation of Blaser et al. and others that acquisition of *H. pylori* infection early in life may lead to a spectrum of gastric pathology, including chronic gastritis, gastric ulcer, gastric metaplasia and increased risk of gastric cancer. Infection later in life may be manifested more in the duodenal pathology and acute antral gastritis (10). Sonnenberg has written about the geographic and temporal variations in the occurrence of peptic ulcer disease. In his studies of different populations, he noted a persistence of disease patterns after migration, and concluded that the determinants of disease probably occur early in life (1). Serologic surveys of the Alaska Native population by Parkinson et al. showed an overall *H. pylori* seroprevalence of 75%, with 90% of positive patients infected before 5 years of age while data from Greenland also indicates a high seroprevalence at an early age (11,12).

In our cohort of patients undergoing EGD, there was a sizable group of patients with evidence of gastritis on histology and endoscopy in which *H. pylori* could not be demonstrated histologically. Indeed, because of the high prevalence of *H. pylori* infection in this cohort and the number of patients examined, a causal relationship between *H. pylori* and gastritis cannot be inferred. These findings differ from recent histologic data from a reinfection cohort of Alaska Native persons with *H. pylori* infection, which demonstrates an association between infection with *H. pylori* and gastritis (Centres for Disease Control, unpublished data). The gastritis in patients involved in our study could not be explained by medication use or other irritants such as alcohol or NSAIDs, and it was similar in histologic appearance to the chronic gastritis noted in patients with *H. pylori* infection. Whether this represents undetected infection or persistence of mucosal changes after eradication is unknown. The reported seroprevalence of 75% in Alaska Native persons is higher than the 65% positivity rate found in this study (11). However, this is expected as serology remains positive for some period following eradication of the organism. A positive serological anti-HP result indicates either active infection or past infection which has been cleared but in which antibody levels remain detectable. In ongoing studies at ANMC on *H. pylori* reinfection, 30% of persons negative for active infection were positive by serologic anti-HP testing. In patients enrolled between 1999 and 2001, 58% were positive for active *H. pylori* infection by histological evaluation, while in this same group, seroprevalence was 42% (13). As previously noted, a representative sample of patient slides was reviewed by an outside laboratory with expertise in
the histological identification of *H. pylori*. They confirmed the accuracy of our institutions’ reports. Unfortunately, serology and urea breath tests were not done on these patients at the time of this study, so we may have underestimated the prevalence of *H. pylori* infection in this cohort.

It has been reported that eradication of *H. pylori* infection is followed by a reversal of the inflammatory changes in the gastric mucosa (14,15). Our observations do not contradict this but do raise the possibility that the histological changes may persist in the absence of the organism or possibly that they may not fully reverse in long-standing infections. Data from research on Mongolian gerbils have demonstrated that complete reversal of inflammatory changes in the stomach may be possible only with early eradication of infection with *H. pylori* (16). Our study was not designed to address this question but does suggest another area for future investigation.

In conclusion, Alaska Native patients undergoing EGD demonstrated a high prevalence of *H. pylori* infection compared with the 35-40% prevalence reported in the general U.S. population (17). The ratio of gastric ulcers to duodenal ulcers at 4:1 is the inverse of that reported in other U.S. populations, but it is similar to that found in other indigenous groups residing in circumpolar regions. Although the incidence of gastric cancer was not an endpoint in this study, the finding of 4 cases of gastric cancer in this cohort is consistent with reports of an increased incidence of gastric cancer in Alaska Native persons, which is greater than 3 times the rate among U.S. Caucasians (4,5). Acquisition of *Helicobacter* infection early in life may be a factor in the relatively increased incidence of gastric pathology, including chronic gastritis, gastric ulcers and gastric cancer seen in this population. In Alaska, further understanding of the natural history of *H. pylori*, including the mechanisms of infection and reinfection, are important elements in developing strategies to deal with this widespread pathogen.

**Acknowledgements**

Thanks to the health care providers in the Departments of Surgery and Internal Medicine at the Alaska Native Medical Center who helped with this study. Special thanks to Tom Hennessy, Alan Parkinson and Anne Lanier for their review of the manuscript.

**REFERENCES**

1. Sonnenberg A. Geographic and temporal variations in the occurrence of peptic ulcer disease. Scand J Gastroenterol Suppl. 1985;110:11-24.
2. Thompson WM, Ackerstein H. Peptic ulcer disease in the Alaska Natives: a four-year retrospective study. Alaska Med. 1975;17(3):43-44.
3. Thompson WM, Ackerstein H. Peptic ulcer disease in the Alaska Natives: a four-year (1967-1971) retrospective study. Alaska Med. 2005;47(1):22.
4. Lanier AP, Kelly JJ, Maxwell J, McEvoy T, Homan C. Cancer in Alaska Native People, 1969-2003. Alaska Med. 2006;48(2):30-59.
5. Alberts SR, Kelly JJ, Lanier AP et al. Occurrence of esophageal and gastric cancer in Alaska Natives, 1969-2003. Alaska Med. 2006;48(1):2-11.
6. Personal correspondence from Dr David Graham, 1994.
7. Leon-Barua R, Recavarren-Arce S. et al. Helicobacter pylori and gastric cancer. Rev. Gastroenterol Peru. 1995; ?? (Suppl 1):S23-27.
8. Fenger HJ, Gudmand-Hoyer E. Peptic ulcer in Greenland Inuit: evidence for a low prevalence of duodenal ulcer. Int J Circumpolar Health 1997;56(3): 64-69.
9. Yip R, Limburg PJ, Ahlquist DA et al. Pervasive occult gastrointestinal bleeding in an Alaska native population with prevalent iron deficiency. Role of Helicobacter pylori gastritis. JAMA. 1997;277(14):1135-1139.
10. Blaser MJ, Chyou PH, Nomura A. Age at establishment of Helicobacter pylori infection and gastric carcinoma, gastric ulcer, and duodenal ulcer risk. Cancer Res. 1995;55(3):562-565.
11. Parkinson AJ, Gold BD, Bulkow L et al. High prevalence of Helicobacter pylori in the Alaska Native population and association with low serum ferritin levels in young adults. Clin Diagn Lab Immunol. 2000;7(6):885-888.
12. Koch A, Krause TG, Krogfelt K, Olsen OR, Fischer TK, Melbye M. Seroprevalence and risk factors for Helicobacter pylori infection in Greenlanders. Helicobacter. 2005;10(5):433-442.
13. Miernyk KM, Bruden DL, Bruce MG et al. Dynamics of Helicobacter pylori-specific Immunoglobulin G for two years after successful eradication of Helicobacter pylori infection in an American Indian and Alaska Native population. Clin Vaccine Immunol. 2007;14(1):00-00.
14. Wong BCy, Lam S, Wong W-M et al. Eradication of Helicobacter pylori infection significantly slows down the progression of precancerous lesions in a high risk population: A 5-year prospective randomized study. Gastroenterology 2002;122:A588.
15. Correa P, Fontham ET, Bravo JC et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. J Natl Cancer Inst. 2000;92(23):1881-1888.
16. Nozaki K, Shimizu N, Ikehara Y et al. Effect of early eradication on Helicobacter pylori-related gastric carcinogenesis in Mongolian gerbils. Cancer Sci. 2003;94(3):235-239.
17. Lacy BE, Rosemore J. Helicobacter pylori; ulcers and more: the beginning of an era. J Nutr. 2001;131:2789S-2793S.

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