Gastric Intestinal Metaplasia in Ethnic Groups in the Southwestern United States

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Abstract

The incidence of gastric cancer has declined dramatically in the United States during this century. However, the incidence of gastric cancer among Hispanics, Blacks, and Native Americans remains 2–3-fold higher than among Whites in this country. Populations with an increased risk of gastric cancer have predominantly the “intestinal” type of gastric cancer, and intestinal metaplasia is regarded as a histological precursor lesion of this type of gastric cancer. We sought to establish the prevalence of intestinal metaplasia, identify associated epidemiological factors, and improve detection of this lesion in a patient population undergoing clinically indicated endoscopy in the Southwestern United States. Among the 440 patients studied, we observed an overall crude prevalence of intestinal metaplasia of 19%. However, the crude prevalence among Hispanics and Blacks was found to be markedly higher than among non-Hispanic Whites (50% versus 13%). Two biopsy protocols (two biopsies versus four biopsies) were used during this study, with a significantly higher rate of intestinal metaplasia detection under the four-biopsy protocol. Adjusting for protocol, we found that age and ethnicity were significantly and independently associated with the prevalence of intestinal metaplasia. The odds of intestinal metaplasia diagnosis was significantly higher in Hispanics compared to non-Hispanic Whites (P < 0.001), and the prevalence of intestinal metaplasia increased with advancing age (P = 0.01). The presence of Helicobacter pylori was also significantly associated with the presence of intestinal metaplasia (P = 0.02), although the direction of the association differed between Hispanics and non-Hispanic Whites.

Introduction

IM is considered to be a precursor lesion in the histological pathway from normal gastric mucosa to gastric cancer (1). Gastric carcinoma is classified into two distinct histological subtypes, the “diffuse” and “intestinal” (2). The intestinal type of gastric carcinoma is more frequently found in populations showing increased risk of gastric cancer and has long been recognized to occur in the background of chronic atrophic gastritis/intestinal metaplasia (3). Intestinal metaplasia develops within areas of chronic atrophic gastritis and is characterized by the replacement of gastric glands by intestinal-type epithelium. In a fraction of the individuals who develop IM, progression to dysplasia and carcinoma is thought to occur (4).

The etiology of IM and intestinal-type gastric cancer remains unclear but presumably involves an interaction of environmental and genetic factors. Diet has been a frequently studied environmental risk factor for gastric carcinoma (4). However, recently the presence of Helicobacter pylori colonization of gastric mucosa has also been implicated as having a possible role in the development of gastric cancer (5–7), and a high prevalence of H. pylori infection has been demonstrated in association with precancerous lesions of the stomach (8).

Although the overall incidence of gastric carcinoma in the United States has been decreasing over the last 60 years, certain ethnic groups continue to be at increased risk for gastric carcinoma (9). These high risk ethnic populations include Blacks, Hispanics, and Native Americans, who have gastric cancer incidence rates 2–3 times higher than those observed among Whites (10, 11). However, the prevalence of IM in these various populations is unknown. We thus conducted a cross-sectional study using upper gastrointestinal endoscopy to determine IM prevalences in an ethnically diverse clinic population in the Southwestern United States.

Materials and Methods

Between 7/1/89 and 7/1/91, subjects were recruited from among patients at one medical center who were undergoing clinically indicated endoscopy of the upper gastrointestinal tract. Patients were excluded if they were undergoing emergency endoscopy, had active bleeding or lesions predisposing to bleeding (e.g., portal gastropathy or varices), or had other contraindications to biopsy. During this time period, a total of 440 patients met the entry criteria for the study, which were reviewed and

1 The abbreviation used is: IM, intestinal metaplasia.
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approved by the human subjects committee at the University of Arizona.

For each patient, key demographic data and the reason for endoscopy were recorded. At the time of endoscopy, the gross appearance of the gastric mucosa was described by the endoscopist performing the procedure. Biopsies were obtained with a standard endoscopic biopsy forceps (Olympus model FB-24K; Olympus Corporation, Lake Success, New York). The gastric mucosa was systematically biopsied according to one of two protocols. Protocol I was used during the first 12 months of the study and required that two biopsies be obtained, both from the angularis along the lesser curvature. Protocol II was used during the second 12 months of the study and required that four biopsies be obtained: two from the angularis plus either (a) one biopsy of the antrum 2 cm distal to the angularis along the lesser curvature or (b) two biopsies of the mid-antrum. Specimens from each patient were pooled and submitted in formalin as a single sample and routinely processed. Special stains (Alcian blue to identify goblet cells, Warthin Starry or Giemsa to identify H. pylori) were used at the discretion of the pathologist. IM was defined as the presence of mucin-containing goblet cells of the intestinal type. The presence of paneth cells and endocrine cells at the base of the crypts was considered supporting evidence (12). The presence or absence of H. pylori by histological examination of the gastric biopsies was also noted.

During the study period, a total of 466 endoscopies were performed on the 440 patients recruited; 26 repeat endoscopies were performed on 25 of the study subjects. For those subjects who had repeat endoscopies, only results from the initial endoscopy are included in the present report.

The data were analyzed using contingency-table analysis, χ² goodness-of-fit tests, and logistic regression analysis (13). Logistic regression techniques were used to model associations between potential predictor variables and the presence of intestinal metaplasia. Odds ratios and 95% confidence intervals were calculated from the resulting model, thereby adjusting for potentially confounding variables. An odds ratio estimates the proportionate change in the odds of IM corresponding to a 1-unit change in a given predictor variable.

Results

The 440 patients studied included 438 males and 2 females (reflecting the predominantly male population of the Veterans Administration Medical Center in Tucson, Arizona), and they ranged from 24 to 94 years of age, with an average age of 63. Reasons for endoscopy included the following: Barrett's/gastroesophageal reflux (n = 164); ulcers/dyspepsia (n = 100); dysphagia (n = 56); anemia/bleeding (n = 46); noncardiac chest pain (n = 18); and miscellaneous (n = 56).

IM was detected in 84 (19%) of the study subjects. Table 1 summarizes the detection of IM according to ethnicity, age, and biopsy protocol; also summarized in Table 1 is the histological presence of H. pylori in relation to ethnicity, age, and biopsy protocol. The detection of IM varied significantly by ethnic group (P < 0.001), with the crude prevalence among Hispanics and Blacks being notably higher than among non-Hispanic Whites (50% versus 13%). Detection was also higher among older age groups, with a significant trend (P = 0.05). Detection rates for the two biopsy protocols were found to differ significantly, with Protocol II detecting IM at more than twice the rate of Protocol I (P < 0.001).

The histological presence of H. pylori also varied significantly by ethnic group (P < 0.001); however, there was no demonstrable age trend for the total study group (P = 0.80). The presence of H. pylori did not vary according to biopsy protocol (P = 0.82).

Age-specific estimates of IM prevalence among Hispanics and non-Hispanic Whites, stratified by protocol, are presented in Table 2. Prevalence estimates within age groups or summarized over age generally revealed the same pattern for both ethnic groups, i.e., IM prevalences estimated by Protocol II were approximately twice that estimated by Protocol I. Of note is that a higher proportion of Hispanics were biopsied under Protocol II as compared to non-Hispanic Whites (74% versus 56%).

Table 3 presents results of fitting a logistic regression model to the data. Because of the significant difference in detection by the two protocols, and because of ethnic differences in the proportions biopsied under each protocol, adjustment for protocol was included in the model.

Table 1 Characteristics of study subjects

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>No. of subjects</th>
<th>No. (%) with intestinal metaplasia</th>
<th>Helicobacter pylori*</th>
</tr>
</thead>
<tbody>
<tr>
<td>White, non-Hispanic</td>
<td>359</td>
<td>47 (13%)</td>
<td>139 (39%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>58</td>
<td>29 (50%)</td>
<td>39 (67%)</td>
</tr>
<tr>
<td>Native American</td>
<td>11</td>
<td>2 (18%)</td>
<td>8 (73%)</td>
</tr>
<tr>
<td>Black</td>
<td>10</td>
<td>5 (50%)</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
</tbody>
</table>

Table 2 Intestinal metaplasia prevalence* by age and ethnicity* with stratification by protocol

<table>
<thead>
<tr>
<th>Age</th>
<th>Protocol I</th>
<th>Total IM+</th>
<th>Protocol II</th>
<th>Total IM+</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>17</td>
<td>2 (12%)</td>
<td>12 (71%)</td>
<td>15</td>
</tr>
<tr>
<td>40-49</td>
<td>53</td>
<td>7 (13%)</td>
<td>21 (40%)</td>
<td>28</td>
</tr>
<tr>
<td>50-59</td>
<td>70</td>
<td>12 (17%)</td>
<td>28 (40%)</td>
<td>30</td>
</tr>
<tr>
<td>60-69</td>
<td>170</td>
<td>31 (18%)</td>
<td>79 (46%)</td>
<td>100</td>
</tr>
<tr>
<td>70-79</td>
<td>111</td>
<td>28 (25%)</td>
<td>46 (41%)</td>
<td>55</td>
</tr>
<tr>
<td>80+</td>
<td>19</td>
<td>4 (21%)</td>
<td>11 (58%)</td>
<td>30</td>
</tr>
</tbody>
</table>

Protocol I (2 biopsies) 179 19 (11%) 79 (44%)
Protocol II (4 biopsies) 261 65 (25%) 118 (45%)

* As detected by histological examination of the biopsy tissue.

* The total number of subjects (Total n) in each category of age, ethnicity, and protocol is tabulated along with the number (n) and percentage (%) demonstrating intestinal metaplasia (IM+) in each category.

* Restricted to Hispanics and non-Hispanic Whites.
The model was also restricted to Hispanics and non-Hispanic Whites because of the numbers available. This model estimates a statistically significant 6-fold increase in the odds of IM for Hispanics compared to non-Hispanic Whites of similar age ($P < 0.001$). The analysis also confirms a significant increase in the prevalence of IM with increasing age, estimating a 3% increase in the odds of detecting IM with each year of age ($P = 0.01$). Under this model we would predict detecting IM in 11% and 15% of Whites 50 and 60 years old, respectively, when using four biopsies as in Protocol II. Corresponding prevalences predicted for Hispanics of the same ages would be 45% and 54%.

We also evaluated a possible association between the histological observation of $H. \text{pylori}$ and the presence of IM. Among all subjects studied, $H. \text{pylori}$ was detected significantly more often in those patients demonstrating IM compared to those patients who did not have IM (56% versus 42%; $P = 0.02$). However, the relationship between IM and $H. \text{pylori}$ varied by ethnic group, as shown in Table 4 for Hispanics and non-Hispanic Whites. Among non-Hispanic Whites, $H. \text{pylori}$ was found more frequently among patients who were IM-positive, but among Hispanics, $H. \text{pylori}$ was found more frequently among patients who were IM-negative. Using a logistic model to adjust for the effects of age and protocol, we observed similar results, i.e., a positive association between the presence of IM and $H. \text{pylori}$ among non-Hispanic Whites (odds ratio = 1.98; $P = 0.03$) and a negative association among Hispanics (odds ratio = 0.34; $P = 0.01$).

### Discussion

This study provides prevalence information on IM in a clinic population in the Southwestern United States. Our data show that IM is not infrequent in a presumably low-risk group of White patients, with a crude prevalence of 13% in the non-Hispanic Whites studied. This prevalence rate is remarkably similar to that seen in a low-risk Italian population studied by endoscopic biopsy (14). Among Hispanic study subjects, a significantly higher crude prevalence of 50% was observed, which is similar to the prevalence of IM observed in studies of other high-risk populations (15). Results also suggested an elevated prevalence among Blacks but not among Native Americans; however, prevalence estimates for patients of these ethnic groups were unstable because of small numbers.

We determined that ethnicity and age were independent risk factors for IM in this clinic population. Hispanics were found to have a significantly greater risk of IM, which is of interest given the higher rate of gastric carcinoma among Hispanics in this country. Increasing age was also significantly related to the risk of IM. The relationship between $H. \text{pylori}$ and IM presence in this patient population was found to vary by race, with a positive association being observed among non-Hispanic Whites and a negative association among Hispanics.

Our study comprised a select group of patients who had symptoms requiring endoscopic evaluation. Selecting subjects from a clinic population in this manner raises the question of whether this study population can be considered to be representative of some larger population with respect to IM prevalence. However, IM is not known to cause symptoms by itself, so it is not clear that such a study population would overestimate IM prevalence. By studying symptomatic patients, we may in fact be underestimating disease prevalence, since gastrointestinal symptoms resulting in diagnostic endoscopy are often related to gastric acidity, which may be diminished in patients with IM. However, if symptoms were indirectly related to IM presence, then some of the observed ethnic difference might be due to ethnic variation in the extent or nature of symptoms at the time of clinic presentation. Further study of asymptomatic subjects seems indicated. Obviously, with this overwhelmingly male study sample, restricting generalizations to males would seem prudent.

We may have underestimated the true prevalence of IM because of our biopsy sampling strategy. We found that increasing the number of biopsies from two to four significantly increased the detection of IM. However, even with four biopsies, it is unlikely that we detected all the patients who actually had IM. Although targeted to areas most likely to yield IM, all biopsies were essentially “blind,” since this lesion is not usually recognizable endoscopically. Indeed, evidence that we have underestimated the true prevalence of IM is provided by data on the patients who had repeat endoscopies during the study period. Twenty-five patients accounted for 26 repeat endoscopies; of the 24 subjects who were negative for IM on initial endoscopy, 2 (8%) were found to have IM when endoscopy was repeated. The optimal number and location of biopsies to maximize the detection of IM cannot be ascertained from the present data. However, based on these data and previous studies indicating that IM is most commonly found distally along the lesser curvature (16), we would recommend that a minimum of four biopsies be obtained: two from the angularis and two from the antrum. Whether or not more biopsies from other regions such as the greater curvature would further

### Table 3 Multivariate model for intestinal metaplasia

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient SE</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td>1.91 0.32</td>
<td>6.74 (3.59, 12.66)</td>
</tr>
<tr>
<td>Age</td>
<td>0.03 0.01</td>
<td>1.03 (1.01, 1.06)</td>
</tr>
<tr>
<td>Protocol</td>
<td>0.86 0.31</td>
<td>2.35 (1.19, 4.29)</td>
</tr>
</tbody>
</table>

* Restricted to Hispanics and non-Hispanic Whites. Covariates in the model are coded as follows: ethnicity (1 = Hispanic, 0 = White, non-Hispanic); age (in years); protocol (1 = Protocol II, 0 = Protocol I).

### Table 4 Presence of Helicobacter pylori in relation to IM status

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>IM+ Total n (%</th>
<th>IM− Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>Protocol I 13 6 (46%)</td>
<td>145 58 (40%)</td>
</tr>
<tr>
<td></td>
<td>Protocol II 34 19 (56%)</td>
<td>167 56 (34%)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>Protocol I 5 3 (60%)</td>
<td>10 8 (80%)</td>
</tr>
<tr>
<td></td>
<td>Protocol II 24 13 (54%)</td>
<td>19 15 (79%)</td>
</tr>
</tbody>
</table>

* The total number of subjects (Total n) in each category of ethnicity, protocol, and IM status is tabulated along with the number (n) and percentage (%) in whom Helicobacter pylori was detected on gastric biopsy (denoted H. pylori+).

IM status: presence of intestinal metaplasia (IM+) or intestinal metaplasia not detected (IM−).
enhance the detection of IM or other pathology cannot be answered from the present data but is worthy of further study.

The role of H. pylori in the epidemiology of IM and gastric carcinoma is unclear. H. pylori may play a part in the initiation of the inflammatory process in the stomach that then results in the development of atrophic gastritis and IM, or it may play a role in the progression of IM into dysplasia and carcinoma. Recent data have indicated that H. pylori is almost universally found in patients demonstrating the intestinal type of gastric carcinoma (5). We cannot determine from the present data whether H. pylori is uniformly found in patients with IM, since histological detection is not the optimal means of documenting H. pylori infection in patients with IM. H. pylori is only found in the presence of gastric epithelium; thus it will not be seen in a biopsy exhibiting diffuse IM with no normal gastric epithelium present, even though it may be present elsewhere in the stomach. Histological means will thus underestimate the true prevalence of H. pylori infection.

We found that the overall prevalence of H. pylori was significantly higher among those with IM than among those in whom IM was not detected. We also found a significantly increased prevalence of H. pylori among patients who were non-White. A surprising finding was the positive association of IM and H. pylori among non-Hispanic Whites but a negative association among Hispanics. Although not readily explainable, one hypothesis is that the higher prevalence of IM in Hispanics may reflect more complete intestinalization of the gastric mucosa. Since we purposely biopsied areas more likely to exhibit IM, in a group with a higher prevalence of IM, histological detection of H. pylori infection may be "masked" by more complete intestinalization. Confirmation of this hypothesis will require further study using better methods to document H. pylori infection. Serological testing for antibody to H. pylori may provide the most accurate means of detecting this infection in patients with IM (17). Longitudinal studies, rather than cross-sectional studies, will be required to elucidate the role of H. pylori in the development of IM.

In summary, IM is not an infrequent finding in patients undergoing diagnostic endoscopy. We found that IM prevalence was significantly higher among Hispanic patients and that IM prevalence increases with the age of the patient. IM was also significantly associated with the presence of H. pylori, with the direction of the association varying by ethnic group. Further study will be required to confirm that the higher prevalence in Hispanic patients reflects a higher prevalence among the asymptomatic Hispanic population and to better understand the natural history of this process in such a population.

References
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