The Association of Helicobacter Pylori with Intestinal Type Gastric Adenocarcinoma in a Hawaii Population*

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American-Japanese in Hawaii with gastric cancer have characteristics intermediate to those in Japan and the mainland United States. Japanese and mainland U.S. studies have found Helicobacter pylori is associated with intestinal type gastric adenocarcinoma. The present Hawaii study confirmed this association which is independent of Japanese race (27.6% intestinal type and 4.5% diffuse type were H. pylori positive, p=0.031, n=80).

Introduction

Recent studies have found an association between *H. pylori* and gastric neoplasm.[1,2] Ninety-five percent of gastric neoplasms are adenocarcinomas.[3] There are two subtypes of gastric adenocarcinomas, the diffuse type and the intestinal type. Intestinal type of gastric adenocarcinomas have goblet cells within the neoplastic tissue and have a better prognosis.[4] These histological subsets were studied specifically by Parsonnet, et al, who discovered that *H. pylori* was present in 89% of intestinal type cases compared with only 32% of diffuse type cases.[5,6] Recently, Parsonnet's findings were confirmed in Japan by Endo, et al, who found that 82% of 34 patients with intestinal type gastric cancer had *H. pylori* compared with 29% of 21 patients with diffuse type.[7] The purpose of this study was to verify the association between H. pylori and intestinal type gastric adenocarcinoma in a Hawaii study population that includes a sizable subpopulation of American-Japanese who are known to have an incidence of gastric cancer intermediate to the native Japanese and mainland U.S. study populations.

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Methods

In a period of 16 months from January 1990 through April 1991, 80 patients with gastric adenocarcinoma were identified through the tumor registries at two Honolulu hospitals, Kaiser Permanente and Kuakini Medical Center. The registries also provided information regarding age, race and sex of these patients.

Pathology slides stained with hematoxylin and eosin (H&E) from the 80 gastric adenocarcinoma cases were examined blindly by one of two examiners (Y.C.). Each patient's set of slides were examined by light microscopy at 100x magnification over 25 fields which included both pericancerous non-neoplastic tissue and neoplastic tissue. The examiner determined the histological type (intestinal or diffuse) of each case.

The examiner also determined the absence or presence of *H. pylori.* A slide positive for *H. pylori* was defined as the presence of 5 or more curvilinear bacilli within a single 100x field. Greater magnification was used as necessary to help identify the *H. pylori* bacilli. This design was selected to reduce false positives. One slide representative of intestinalization without *H. pylori* and a second slide of *H. pylori* without intestinalization, were inserted with each set of slides as controls.

All *H. pylori* positive slides and an equal number of randomly selected *H. pylori* negative slides from the same hospital were identified. These slides were randomized and re-examined by a second blinded observer using the same technique mentioned above (H.C.).

Statistical analyses were performed using SPSS (Statistical Package for Social Sciences version 4.2).

Results

Fifty-eight of the 80 adenocarcinoma cases (73%) were of the intestinal type, while the remaining 22 cases (27%) were of the diffuse histological type. Table 1 shows that *H. pylori* was present in 16 of the 58 intestinal cases (27.6%) compared with only one of the 22 diffuse cases (4.5%), a difference which was statistically significant (Fisher's exact test: p=0.031).

A comparison of cases with and without *H. pylori* by age, gender, hospital site and Japanese race is presented in Table 2. None of the comparisons was statistically significant.

The reexamination by a second blinded examiner of 17 *H. pylori* positive cases and 17 randomly selected negative cases, stratified by hospital, showed complete agreement between the two observers. This resulted in a Cohen's kappa coefficient of 1.00 ($p < 0.001$). Controls were correctly identified 100% of the time in both the

Table 1.—The Relationship of *Helicobacter pylori* to Gastric Adenocarcinoma

	Histological Type	
	Intestinal Type # of cases (%)	Diffuse Type # of cases (%)
H. pylori Present	16 (27.6%)	1 (4.5%)
H. pylori Absent	42 (72.4%)	21 (95.5%)
Total	58 (100%)	22 (100%)

original trial and the validity trial.

Discussion

The present study found a statistically significant relationship between *H. pylori* and intestinal type gastric adenocarcinoma which is consistent with previous studies.[5-7] The study's stringent criteria for *H. pylori* positivity resulted in a prevalence less than that of previous reports. In contrast to previous studies, no significant relationship between age and *H. pylori* was found using cutoffs of 50, 55, 60, 65 and 70 years of age.[2] This result may be due to the preponderance of subjects similar in age; 88% of the study population was 60+ y.o.

This Hawaii study is unique in that it represents an American-Japanese population with a gastric cancer mortality rate that is in between those of Japan and the mainland United States. Gastric cancer is the second leading cause of cancer mortality in Hawaii among American-Japanese males with an age adjusted mortality rate of 15.9 per 100,000.[8] In Japan, the male age adjusted mortality rate is 32.8 per 100,000 whereas in the United States this mortality rate is 5.0 per 100,000. Gastric cancer is the most common cause of cancer mortality in Japan compared to being the 7th most common cause of cancer deaths in the United States.[9] Parsonnet's study was carried out on the West Coast of the United States where there is a small Japanese population whereas Endo's study in Japan was of a Japanese population. American-Japanese comprise 22% of Hawaii's population, but 76.3% of the present study's population.[10] Parsonnet's and Endo's results show similar *H. pylori* prevalence in their study population despite different Japanese populations which would suggest that *H. pylori* positivity was not associated with Japanese race. This was consistent with the present study which found that *H. pylori* positivity was not associated with Japanese race (see Table 2).

Another Hawaii study published by Nomura found the presence of anti-*H. pylori* IgG antibodies in 94% of the stored serum samples belonging to 109 American-Japanese males who developed gastric carcinoma. This case-control study showed that gastric cancer is associated with *H. pylori* in both the intestinal and diffuse subgroups. Intestinalization was found to be present in 73.0% of Nomura's population compared to 72.5% in the present study's population. This suggests that the two populations are similar. Despite having similar American-Japanese populations, it is not possible to compare Nomura's *H. pylori* antibody study to the present light microscopy study. The present study detected the presence of *H. pylori* by biopsy at the time of discovery of the cancer whereas the antibody assay for *H. pylori* only indicates exposure to this pathogen. In a stored serum study, it is possible to miss cases of *H. pylori* associated with gastric cancer if infection occurred after the serum was drawn. The average time between phlebotomy and cancer diagnosis was 13 years in the stored serum study. Another problem is that antibody titers may also become negative if *H. pylori* disappeared more than 1 year prior to sampling. On the other hand, in a light microscopy study, it is possible to miss cases of *H. pylori* associated with cancer where the pathogen disappeared after the cancer developed or where an inadequate stain is used. The neoplastic tissue, especially of the diffuse type, may present an environment hostile to *H. pylori* growth.[1]

Table 2.—*Helocobacter pylori* and Various Characteristics Among Gastric Adenocarcinoma Cases

Characteristic	H. pylori Present	H. pylori Absent	Odds Ratio	95% Confidence Limit
Histology				
Intestinal type	16	42		
Diffuse type*	1	21	8.00	1.07, 351
Hospital				
Kuakini	16	50		
Kaiser*	1	13	4.16	0.53, 187
Age (years)				
>60	13	57		
≤60*	4	6	0.34	0.07, 1.92
Gender				
female	8	25		
male*	9	38	1.35	0.40, 4.50
Race				
Japanese	14	47		
Non-Japanese*	3	16	1.59	0.37, 9.67

* = Referent Group

In summary, this Hawaii study confirms the relationship between *H. pylori* and intestinal type gastric adenocarcinoma as found in studies in Japan and the mainland United States. The association between *H. pylori* and intestinal type adenocarcinoma was not affected by age, gender, institution, or Japanese race.

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