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

Hausen Cheong MD, Patti Char MS, Yuan Chang MS, Stanley S. Shimoda MD

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.

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

* Division of Gastroenterology
Department of Internal Medicine
John A. Burns School of Medicine
University of Hawaii at Manoa
Kaiser Permanente Hospital
Moanalua
Kuakini Medical Center

Address Reprint Request to:
Stanley S. Shimoda, M.D.,
Division of Gastroenterology,
Department of Internal Medicine
321 North Kuakini St., Suite #503,
Honolulu Hawaii 96817

	Histological Type	
	Intestinal Type # of cases (%)	Diffuse Type # of cases (%)
<i>H. pylori</i> Present	16 (27.6%)	1 (4.5%)
<i>H. pylori</i> 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

Characteristic	<i>H. pylori</i> Present	<i>H. pylori</i> 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

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

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.

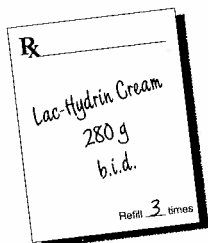
Acknowledgments

The authors thank the late Takuji Hayashi MD, Kuakini Medical Center, Department of Pathology for his help with this project. Thanks also to Stanley Loo MD, Kaiser Permanente, Department of Pathology; Abraham Nomura MD, Kuakini Medical Center, Japan-Hawaii Cancer Study; and Cyrus E. Rubin MD, University of Washington, Division of Gastroenterology for their assistance.

References

- Nomura A, Stemmermann G, Chyou P, Kato I, Perez-Perez GI, Blaser MJ. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. *N Eng J Med*. 1991; 325: 1132-1136.
- Eurogast Study Group. An International Association Between *Helicobacter pylori* Infection and Gastric Cancer. *Lancet*. 1993; 341: 1359-1362.
- Parsonnet J, Friedman GD, Vandersteen DP, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Eng J Med*. 1991; 325: 1127-1131.

You have to write it to get it.



CAUTION: Federal law prohibits dispensing without a prescription.

Lac-Hydrin® 12%* (ammonium lactate cream) Cream

For Dermatologic use only. Not for ophthalmic, oral or intravaginal use.

DESCRIPTION: Lac-Hydrin is a formulation of 12% lactic acid neutralized with ammonium hydroxide, as ammonium lactate, with a pH of 4.4-5.4. Lac-Hydrin Cream also contains water, light mineral oil, glyceryl stearate, polyoxyl 100 stearate, propylene glycol, polyoxyl 40 stearate, glycerin, cetyl alcohol, magnesium aluminum silicate, laureth-4, methyl and propyl parabens, methylcellulose, and quaternium-15. Lactic acid is a racemic mixture of 2-hydroxypropanoic acid and has the following structural formula:



CLINICAL PHARMACOLOGY: Lactic acid is an alpha-hydroxy acid. It is a normal constituent of tissues and blood. The alpha-hydroxy acids (and their salts) are felt to act as humectants when applied to the skin. This property may influence hydration of the stratum corneum. In addition, lactic acid, when applied to the skin, may act to decrease corneocyte cohesion. The mechanism(s) by which this is accomplished is not yet known.

An *in vitro* study of percutaneous absorption of Lac-Hydrin Cream using human cadaver skin indicates that approximately 6.1% of the material was absorbed after 68 hours.

INDICATIONS AND USAGE: Lac-Hydrin Cream is indicated for the treatment of ichthyosis vulgaris and xerosis.

CONTRAINDICATIONS: None known.

WARNING: Use of this product should be discontinued if hypersensitivity to any of the ingredients is noted. Sun exposure (natural or artificial sunlight) to areas of the skin treated with Lac-Hydrin Cream should be minimized or avoided (see Precautions section).

PRECAUTIONS: General: For external use only. Stinging or burning may occur when applied to skin with fissures, erosions, or that is otherwise abraded (for example, after shaving the legs). Caution is advised when used on the face because of the potential for irritation. The potential for post-inflammatory hypo- or hyperpigmentation has not been studied.

Information for patients: Patients using Lac-Hydrin Cream should receive the following information and instructions:

1. This medication is to be used as directed by the physician, and should not be used for any disorder other than for which it was prescribed. Caution is advised when used on the face because of the potential for irritation. It is for external use only. Avoid contact with eyes, lips, or mucous membranes.
2. Patients should minimize or avoid use of this product on areas of the skin that may be exposed to natural or artificial sunlight, including the face. If sun exposure is unavoidable, clothing should be worn to protect the skin.
3. This medication may cause stinging or burning when applied to skin with fissures, erosions, or abrasions (for example, after shaving the legs).
4. If the skin condition worsens with treatment, the medication should be promptly discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: A long-term phototoxicity study in hairless albino mice suggested that topically applied 12% ammonium lactate cream enhanced the rate of ultraviolet light-induced skin tumor formation. Although the biologic significance of these results to humans is not clear, patients should minimize or avoid use of this product on areas of the skin that may be exposed to natural or artificial sunlight, including the face. Long-term dermal carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of ammonium lactate.

Pregnancy: Teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Lac-Hydrin Cream. It is also not known whether Lac-Hydrin Cream can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Lac-Hydrin Cream should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Although lactic acid is a normal constituent of blood and tissues, it is not known to what extent this drug affects normal lactic acid levels in human milk. Because many drugs are excreted in human milk, caution should be exercised when Lac-Hydrin Cream is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of Lac-Hydrin Cream have not been established in pediatric patients less than 12 years old. Potential systemic toxicity from percutaneous absorption has not been studied. Because of the increased surface area to body weight ratio in pediatric patients, the systemic burden of lactic acid may be increased.

ADVERSE REACTIONS: In controlled clinical trials of patients with ichthyosis vulgaris, the most frequent adverse reactions in patients treated with Lac-Hydrin Cream were rash (including erythema and irritation) and burning/stinging. Each was reported in approximately 10-15% of patients. In addition, itching was reported in approximately 5% of patients.

In controlled clinical trials of patients with xerosis, the most frequent adverse reactions in patients treated with Lac-Hydrin Cream were transient burning, in about 3% of patients, stinging, dry skin and rash, each reported in approximately 2% of patients.

DOSAGE AND ADMINISTRATION: Apply to the affected areas and rub in thoroughly. Use twice daily or as directed by a physician.

HOW SUPPLIED: Lac-Hydrin Cream is available in cartons of 280 g (2-140 g plastic tubes). Store at controlled room temperature, 15-30°C (59-86°F).



©1994 WESTWOOD-SQUIBB
PHARMACEUTICALS INC.
Buffalo, N.Y., U.S.A. 14213
A Bristol-Myers Squibb Company

03-5982-1
Revised August 20, 1996

4. Lauren, P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. *Acta Pathol et Microbiol Scand.* 1965; 64: 31-49.
5. Parsonnet J. *Helicobacter pylori* and Gastric Cancer. *Gastroenterol Clin North Am.* 1993; 22: 89-104.
6. Parsonnet J, Vandersteen D, Goates J, Sibley RK, Pritikin J, Chang Y. *Helicobacter pylori* infection in intestinal- and diffuse- type gastric adenocarcinomas. *J Natl Cancer Inst.* 1991; 9: 640-643.
7. Endo S, Ohkusa T, Okayasu I, Tamura Y, Saito Y. Detection of *Helicobacter pylori* in early gastric cancer: comparison between intestinal and diffuse type gastric adenocarcinomas. *Gastroenterology.* 1992; 102 (part 2): A64.
8. Hawaii Tumor Registry. Age-adjusted incidence and mortality rates (per 100,000) by ethnicity and sex, Hawaii, 1983-1986. Honolulu. Hawaii Tumor Registry, 1991.
9. Parker S, Tong T, Bolden S, Wingo PA. Cancer Statistics, 1997. *CA Cancer J Clin.* 1997; 1: 5-27.
10. State Department of Health, Health Surveillance Program. State of Hawaii 1986 Ethnic percentage distribution. In: Oyama NM, ed. State of Hawaii Native Hawaiian Health Data Book 1990. Honolulu. Office of Hawaiian Affairs, 1990.



HAWAII
PATHOLOGISTS'
LABORATORY

The Full Service Lab

Offering Comprehensive
Services in..

- Clinical Pathology
- Surgical Pathology
- Frozen Section Diagnosis
- Pap Smears
- Special Cytology
- Flow Cytometry
- Fine Needle Aspiration
- Bone Marrow Interpretation
- Specimen Photography
- Image Analysis

1301 Punchbowl Street
Honolulu, Hawaii 96813
547-4271 Fax 547-4045

