Chronic Atrophic Gastritis and *Helicobacter pylori* Infection among Japanese Americans in Seattle

Tsukasa Namekata,[1,2] Kazumasa Miki,[3] Michael Kimmey,[4] Thomas Fritsche,[5] Deborah Hughes,[1] David Moore,[6] and Kenji Suzuki[7]

Gastric cancer is still a major cause of mortality due to cancer worldwide. The most common type of gastric cancer is intestinal type carcinoma, which usually occurs in stomachs containing chronic atrophic gastritis. Individuals with chronic atrophic gastritis are considered to be at increased risk for developing intestinal type carcinoma of the stomach. To examine the association between chronic atrophic gastritis and other gastric cancer risk factors, a cross-sectional study was conducted using serum samples and questionnaire information collected from 776 persons of full Japanese ancestry in the greater Seattle area in 1994. The presence of chronic atrophic gastritis and *Helicobacter pylori* infection was determined by measurement of serum pepsinogen levels and *H. pylori* antibodies, respectively. Based on multiple logistic regression, the significant predictors of chronic atrophic gastritis were age over 50 years, *H. pylori* infection, and 20 years or more lived in Japan. Alcohol consumption, smoking, prior peptic ulcer, and history of gastric cancer in parents were not significantly associated with chronic atrophic gastritis. The results imply that *H. pylori* infection since earlier life and other unknown exposure factors in Japan might have played an important role in the development of chronic atrophic gastritis. *Am J Epidemiol* 2000;151:820–30.

gastritis, atrophic; *Helicobacter pylori*; life style; pepsinogens; smoking

Despite the recent decline in the incidence of gastric cancer, it remains a major cause of cancer mortality worldwide (1), with one of the highest rates found in Japan and one of the lowest in the United States (2). The decline in gastric cancer rates can be attributed mainly to a decrease in the incidence of intestinal type carcinoma, whereas there has been little, if any, decrease in diffuse type carcinoma (3–5). Numerous studies have indicated that intestinal type carcinoma is strongly influenced by environmental factors, and the shifts that have occurred are thought to be a conse-

quence of changes in dietary and environmental factors that contribute to carcinogenesis (6). In addition to age, the two most contributory factors to the development of intestinal type carcinoma are considered to be a diet that is high in salt and low in fresh fruits and vegetables and chronic infection with *Helicobacter pylori* (6, 7).

As first hypothesized by Correa (8), chronic atrophic gastritis is considered to be a preceding condition in the sequential histopathologic changes that lead to intestinal type gastric carcinoma. Therefore, persons with chronic atrophic gastritis are considered to have a higher risk for developing gastric cancer than those without such a condition. With the development of radioimmunoassay for pepsinogen I (PG I) and pepsinogen II (PG II), it has been reported that the PG I/PG II ratio in combination with the level of PG I predicted the presence of atrophic gastritis (9–11), and thus the method has been used in Japan as a serum marker to screen individuals at high risk for gastric cancer who are then recommended for endoscopic examination (12–14).

Since the first reports on gastric colonization by *H. pylori* in the early 1980s (15, 16), it has been established that *H. pylori* infection is strongly associated with peptic ulcer disease (17–20) and chronic atrophic gastritis and intestinal metaplasia (21–23). *H. pylori* strains possessing the cytotoxin-associated gene A

(*cagA*) are considered to enhance induction of acute inflammation leading to the development of atrophic gastritis and gastric cancer (21). Early life acquisition of *H. pylori* has been considered to increase the risk of developing both gastric cancer and gastric ulcer (20). A growing body of research suggests a link between *H. pylori* infection and gastric carcinoma (21–26). Furthermore, ecologic studies show a significant relation between the prevalence of *H. pylori* infection and gastric cancer incidence and mortality (27) and an association between the prevalence of chronic atrophic gastritis and the standard mortality ratio for gastric cancer (28). There must be additional risk factors that play an important role in the causation of gastric cancer, since only a small proportion of persons infected with *H. pylori* develop gastric carcinoma.

The investigators hope to shed some light on the role of *H. pylori* in the development of gastric cancer by examining the relation between chronic atrophic gastritis and *H. pylori* infection among Japanese Americans. This is an important population to study because they share a common genetic background with native Japanese, who suffer one of the highest gastric cancer mortality rates of all populations, but live in the nation where gastric cancer mortality is the lowest in the world (2).

The present study estimated the prevalence of chronic atrophic gastritis by using the serum pepsinogen method and the presence of immunoglobulin G antibodies to *H. pylori* infection among Japanese Americans in Seattle, Washington. The associations of possible risk factors with *H. pylori* infection and chronic atrophic gastritis were also examined.

MATERIALS AND METHODS

The study sample consisted of male and female Japanese Americans residing in the greater Seattle area (King County) who participated in cardiovascular disease screening conducted by the Pacific Rim Disease Prevention Center in 1994. The screening participants were respondents from a media and family registration campaign. Completed clinical and survey information was collected from a total of 415 males and 361 females of full Japanese ancestry between the ages of 20 and 86 years. The composition of the study sample with respect to generation was as follows: 12.9 percent Issei (first generation), 41.4 percent Nisei (second generation), 44.1 percent Sansei (third generation), and 1.7 percent Yonsei (fourth generation), as shown in table 1.

Due to the fact that the study subjects were voluntary participants, an additional survey on 1994 household income levels was conducted to better define our study sample characteristics and examine whether they were

TABLE 1. Study sample characteristics of Japanese Americans, Seattle, Washington, 1994

	Males, n = 415 (%)	Females, n = 361 (%)
Age (years)		
<50	38.1	41.8
50–64	32.8	32.1
65–74	21.0	20.8
≥75	8.2	5.3
Generation in United States		
First	9.4	16.9
Second	44.8	37.4
Third	43.9	44.3
Fourth	1.9	1.4
Lived in Japan (years)		
<1	70.1	65.4
1–9	13.0	13.6
10–19	7.5	5.5
≥20	9.4	15.5
Alcohol drinking		
Nondrinkers	12.0	28.0
Former drinkers	20.5	17.7
Current drinkers	67.5	54.3
Smoking		
Nonsmokers	41.0	70.1
Former smokers	46.0	21.9
Current smokers	13.0	8.0
History of peptic ulcer	10.4	6.1
Parental history of gastric cancer	3.1	4.4
Helicobacter pylori infection	27.5	29.1

representative of the Japanese American population in the Seattle area. Of the 776 study participants, 82.0 percent responded to the survey. The household incomes from the study participants were compared with those of Japanese American households in the 1990 census for King County (29). Figure 1 shows that the income distribution of the screening participants was slightly higher than that reported for the Japanese American population in King County for the 1990 census.

Venous blood samples were obtained after a 12-hour fast from study participants in 1994. Two ml of sera were stored at −70°C. Serum samples were thawed and divided into two aliquots for analysis of serum pepsinogen levels and *H. pylori* antibodies. Serum PG I and PG II levels were measured using Riabead kits (Dainabot Co., Tokyo, Japan) (30), and subjects with chronic atrophic gastritis were defined as those with a PG I level of <70 μg/liter and a PG I/PG II ratio of <3.0. The presence of *H. pylori* antibodies was determined using an immunoglobulin G enzyme-linked
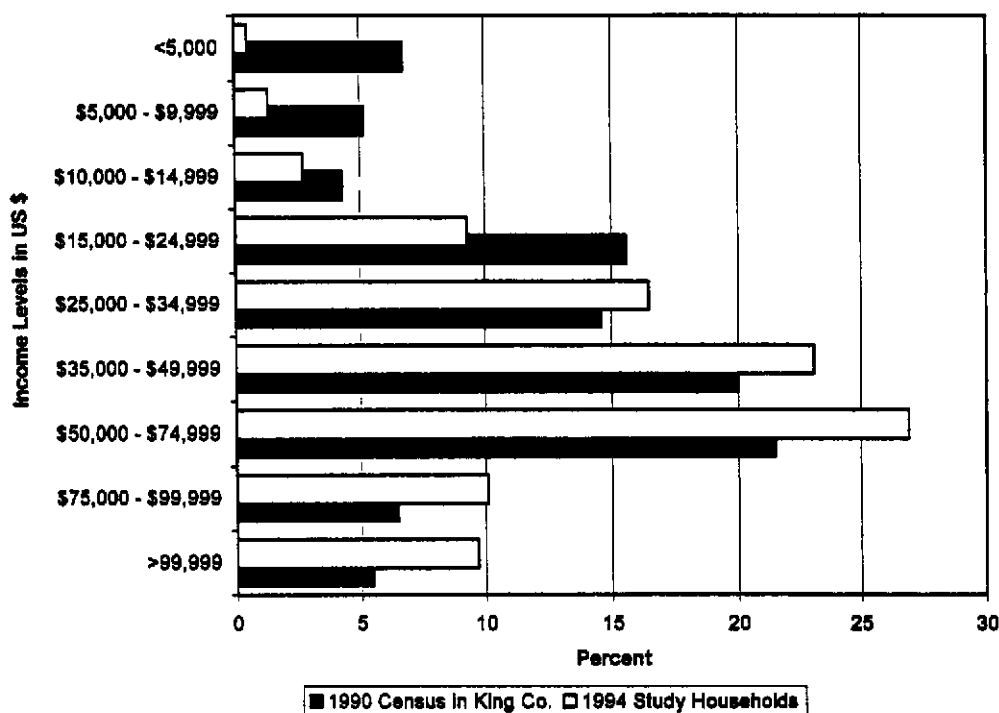
FIGURE 1. Comparison of income distributions of Japanese Americans between the 636 households that participated in the study in 1994 and the 8,518 households in King County, Washington, from the 1990 US census.

immunosorbent assay for *H. pylori* (Bio-Rad Laboratories, Anaheim, California) (31, 32). Specimens tested having greater than 12.5 units/ml for immunoglobulin G antibodies were considered to be positive for *H. pylori* infection.

Surveys, self-administered at the time of screening, contained questions on personal and demographic background, medical history, and lifestyle habits such as alcohol consumption and smoking. Those who had never or rarely (less than once per month) consumed alcoholic beverages were classified as nondrinkers.

Two analyses with multiple logistic regression were conducted: to predict seropositivity of *H. pylori* infection by age, years lived in Japan, alcohol consumption, smoking status, history of ulcer, and family history of gastric cancer; and to predict the presence of chronic atrophic gastritis as determined with low serum pepsinogen levels by the same factors as above and *H. pylori* infection. Analyses were conducted separately by sex and generation using SPSS/PC+ V8.0 software (SPSS, Inc., Chicago, Illinois) (33).

RESULTS

Characteristics of the study subjects are presented in table 1. More than 60 percent of the subjects were older than 50 years old. The majority of the study sam-

ple had never lived in or had spent less than 1 year in Japan (70 percent of men and 65 percent of women). Seropositivity for *H. pylori* infection was found to be 27.5 percent for men and 29.1 percent for women. The prevalences of *H. pylori* infection and chronic atrophic gastritis were similar between men and women and increased steadily with age (table 2).

The results of multiple logistic regression analysis to predict seropositivity of *H. pylori* with age, years lived in Japan, alcohol consumption, smoking, history of ulcer, and parental death due to gastric cancer are presented in table 3. No great discrepancy is observed between crude and adjusted odds ratios. Significant odds ratios were observed in both men and women for increasing age (with the exception of men over the age of 75 years), having lived in Japan for more than 20 years for men (odds ratio (OR) = 5.12, 95 percent confidence interval (CI): 2.44, 10.69) and for women (OR = 2.80, 95 percent CI: 1.45, 5.39), and past history of peptic ulcer for men (OR = 2.88, 95 percent CI: 1.42, 5.83) and for women (OR = 4.30, 95 percent CI: 1.54, 12.03). Current smoking habit and past smoking habit were associated with an increased risk for *H. pylori* infection in men only (OR = 2.39, 95 percent CI: 1.14, 5.03; and OR = 1.77, 95 percent CI: 1.00, 3.14, respectively). Alcohol consumption and family history (death of either parent due to gastric

TABLE 2. Prevalence of *Helicobacter pylori* infection and chronic atrophic gastritis among Japanese Americans, Seattle, Washington, 1994

	H. pylori seropositive				Chronic atrophic gastritis			
	Males		Females		Males		Females	
	No. of cases	%	No. of cases	%	No. of cases	%	No. of cases	%
Age (years)								
<50	24	15.2	23	15.2	4	2.5	3	2.0
50–64	45	33.1	38	32.8	20	14.7	18	15.5
65–74	31	35.6	33	44.0	24	27.6	15	20.0
≥75	14	41.2	11	57.9	12	35.3	7	36.8
Chi-square test for trend	$p < 0.0001$		$p < 0.0001$		$p < 0.0001$		$p < 0.0001$	

cancer) were not found to be associated with *H. pylori* infection.

To examine the difference in the association of *H. pylori* infection with biologic and lifestyle factors between the first generation and the second to fourth generation of Japanese Americans, we computed the odds ratios again for the two groups (table 4). Only having the past diagnosis of peptic ulcer was significantly associated with *H. pylori* infection (OR = 16.62, 95 percent CI: 1.84, 150.05) in the first gener-

TABLE 3. Odds ratios for *Helicobacter pylori* infection by sex among Japanese Americans, Seattle, Washington, 1994

	Males				Females			
	No. of cases of H. pylori infection	Crude OR*	Adjusted OR†	95% CI*	No. of cases of H. pylori infection	Crude OR	Adjusted OR†	95% CI
Age (years)								
<50	24	1.00	1.00		23	1.00	1.00	
50–64	45	2.76	1.93	1.03, 3.60	38	2.71	2.42	1.27, 4.57
65–74	31	3.09	2.16	1.06, 4.40	33	4.37	3.73	1.82, 7.68
≥75	14	3.91	2.55	0.98, 6.61	11	7.65	8.33	2.74, 25.31
Lived in Japan (years)								
<1	62	1.00	1.00		62	1.00	1.00	
1–9	16	1.56	1.13	0.56, 2.29	11	0.81	0.77	0.34, 1.72
10–19	13	2.67	2.09	0.93, 4.71	5	0.94	0.88	0.28, 2.75
≥20	23	5.31	5.12	2.44, 10.69	27	2.61	2.80	1.45, 5.39
Drinking status								
Nondrinkers	15	1.00	1.00		36	1.00	1.00	
Former drinkers	23	0.87	0.98	0.41, 2.34	13	0.46	0.95	0.42, 2.20
Current drinkers	76	0.87	1.05	0.50, 2.24	56	0.72	1.47	0.80, 2.73
Smoking status								
Nonsmokers	29	1.00	1.00		76	1.00	1.00	
Former smokers	65	2.51	1.77	1.00, 3.14	24	1.02	0.93	0.50, 1.75
Current smokers	20	2.86	2.39	1.14, 5.03	5	0.49	0.36	0.12, 1.08
History of peptic ulcer								
No	91	1.00	1.00		90	1.00	1.00	
Yes	23	3.55	2.88	1.42, 5.83	15	5.93	4.30	1.54, 12.03
Parental history of gastric cancer								
No	107	1.00	1.00		96	1.00	1.00	
Yes	7	3.22	1.93	0.58, 6.42	9	3.33	1.69	0.54, 5.30

* OR, odds ratio; CI, confidence interval.

† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, and parental history of gastric cancer.

TABLE 4. Odds ratios for *Helicobacter pylori* by generation among Japanese Americans, Seattle, Washington, 1994

	First generation				Second to fourth generation			
	No. of cases of *H. pylori* infection	Crude OR*	Adjusted OR†	95% CI*	No. of cases of *H. pylori* infection	Crude OR	Adjusted OR†	95% CI
Female								
No	22	1.00	1.00		92	1.00	1.00	
Yes	28	0.66	0.61	0.23, 1.67	77	1.07	1.30	0.87, 1.95
Age (years)								
<50	14	1.00	1.00		33	1.00	1.00	
50–64	28	2.63	2.31	0.84, 6.31	55	2.63	2.28	1.37, 3.78
≥65	8	2.38	2.12	0.49, 9.20	81	4.85	3.89	2.32, 6.50
Lived in Japan (years)								
<10	2	1.00	1.00		149	1.00	1.00	
10–19	7	1.31	0.48	0.05, 4.93	11	1.41	1.12	0.52, 2.39
≥20	41	1.58	0.86	0.12, 6.23	9	4.79	3.65	1.22, 10.94
Smoking status								
Nonsmokers	28	1.00	1.00		77	1.00	1.00	
Former smokers	17	1.26	0.86	0.30, 2.51	72	1.62	1.29	0.83, 2.01
Current smokers	5	0.48	0.35	0.09, 1.41	20	1.57	1.57	0.83, 2.97
Drinking status								
Nondrinkers	13	1.00	1.00		38	1.00	1.00	
Former drinkers	6	0.92	1.06	0.22, 5.23	30	0.64	0.88	0.47, 1.64
Current drinkers	31	1.15	0.99	0.32, 3.01	101	0.73	1.11	0.67, 1.86
History of peptic ulcer								
No	39	1.00	1.00		142	1.00	1.00	
Yes	11	13.82	16.62	1.84, 150.05	27	3.52	2.40	1.30, 4.43
Parental history of gastric cancer								
No	47	1.00	1.00		156	1.00	1.00	
Yes	3	3.13	2.40	0.20, 28.3	13	3.44	1.76	0.74, 4.16

* OR, odds ratio; CI, confidence interval.
† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, and parental history of gastric cancer.

ation group. For the second to fourth generation group, on the other hand, odds ratios were significantly elevated in ages greater than 50 years: 50–64 years (OR = 2.28, 95 percent CI: 1.37, 3.78) and 65 years and over (OR = 3.89, 95 percent CI: 2.32, 6.50), living in Japan for 20 years and longer (OR = 3.65, 95 percent CI: 1.22, 10.94), and having the past diagnosis of peptic ulcer (OR = 2.40, 95 percent CI: 1.30, 4.43).

Table 5 presents the results of multiple logistic regression analysis to predict the presence of chronic atrophic gastritis. The risk of chronic atrophic gastritis increased steadily with age for both men and women. Significant odds ratios were also observed for living in Japan for 1–9 years for men (OR = 2.98, 95 percent CI: 1.22, 7.26) and living in Japan for more than 20 years for men (OR = 8.30, 95 percent CI: 3.13, 21.76) and for women (OR = 3.32, 95 per-

cent CI: 1.32, 8.34) and *H. pylori* infection for men (OR = 9.63, 95 percent CI: 4.55, 20.18) and for women (OR = 16.31, 95 percent CI: 6.18, 42.87). Current or past smoking and drinking habits and history of peptic ulcer were not associated with chronic atrophic gastritis. Similarly, death due to gastric cancer of either parent was not found to be associated with chronic atrophic gastritis. When multiple logistic regression analysis was done by generation (table 6), the results are almost the same as those in table 5, except that the longer duration lived in Japan was not significantly associated with chronic atrophic gastritis in the first generation, while it remained significant in the second to fourth generation (20 years or more lived in Japan: OR = 6.96, 95 percent CI: 1.69, 28.65).

To examine the possibility that the areas of severe atrophy and intestinal metaplasia can be hostile to *H.*

TABLE 5. Odds ratios for chronic atrophic gastritis by sex among Japanese Americans, Seattle, Washington, 1994

	Males				Females			
	No. of cases of chronic atrophic gastritis	Crude OR*	Adjusted OR†	95% CI*	No. of cases of chronic atrophic gastritis	Crude OR	Adjusted OR†	95% CI
Age (years)								
<50	4	1.00	1.00		3	1.00	1.00	
50–64	20	6.64	5.67	1.61, 19.95	18	9.06	6.05	1.47, 24.42
65–74	24	14.67	14.88	4.10, 54.04	15	12.33	7.80	1.72, 35.00
≥75	12	21.00	26.62	5.95, 119.27	7	28.78	18.12	3.05, 108.16
Lived in Japan (years)								
<1	23	1.00	1.00		23	1.00	1.00	
1–9	14	4.08	2.98	1.22, 7.26	1	0.19	0.15	0.02, 1.23
10–19	5	2.24	1.36	0.41, 4.50	2	1.03	0.78	0.12, 4.89
≥20	18	9.99	8.30	3.13, 21.76	17	4.04	3.32	1.32, 8.34
Drinking status								
Nondrinkers	10	1.00	1.00		20	1.00	1.00	
Former drinkers	12	0.66	1.46	0.45, 4.71	4	0.27	0.73	0.18, 3.02
Current drinkers	38	0.63	0.61	0.47, 3.62	19	0.43	0.73	0.31, 1.76
Smoking status								
Nonsmokers	16	1.00	1.00		32	1.00	1.00	
Former smokers	36	2.24	0.76	0.32, 1.80	9	0.89	1.18	0.19, 6.04
Current smokers	8	1.67	0.76	0.24, 2.42	2	0.51	1.06	0.43, 3.26
History of peptic ulcer								
No	52	1.00	1.00		37	1.00	1.00	
Yes	8	1.41	0.47	0.17, 1.31	6	3.06	1.03	0.30, 3.46
Parental history of gastric cancer								
No	56	1.00	1.00		40	1.00	1.00	
Yes	4	2.75	0.69	0.15, 3.23	3	1.76	0.69	0.00, 0.03
***Helicobacter pylori* infection**								
No	16	1.00	1.00		6	1.00	1.00	
Yes	44	11.20	9.63	4.55, 20.18	37	22.67	16.31	6.18, 42.87

* OR, odds ratio; CI, confidence interval.

† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, parental history of gastric cancer, and *H. pylori* infection.

pylori colonization (34–36), we explored further the analysis of the level of PG I and the PG I/PG II ratios in relation to *H. pylori* status in the 103 subjects with chronic atrophic gastritis. In this group, 22 were seronegative for *H. pylori* and 81 subjects were seropositive. The mean PG I/PG II ratio in subjects with chronic atrophic gastritis and seronegative for *H. pylori* (mean = 1.30) was significantly lower than the mean PG I/PG II ratio among seropositive subjects (mean = 2.00) ($p < 0.0001$). Similarly, the mean level of PG I in subjects with chronic atrophic gastritis and seronegative for *H. pylori* (mean = 18.5 ng/liter) was significantly lower than the mean PG I level among seropositive subjects (mean = 39.0 ng/liter) ($p < 0.0001$).

DISCUSSION

One potential bias in the present study is that the sample was not randomly drawn from the Japanese American population in the Seattle area, and nonparticipants may have different characteristics and health status from those of the participants. Other surveys have shown that nonparticipants had poorer health than did participants (37). In order to examine this issue further, we conducted an additional survey to determine the 1994 annual household income levels of our study sample and compared their income distribution with that of Japanese American households in King County from the 1990 US census (which includes Seattle and the surrounding metropolitan

TABLE 6.   Odds ratios for chronic atrophic gastritis by generation among Japanese Americans, Seattle, Washington, 1994

	First generation				Second to fourth generation			
	No. of cases of chronic atrophic gastritis	Crude OR*	Adjusted OR†	95% CI*	No. of cases of chronic atrophic gastritis	Crude OR	Adjusted OR†	95% CI
Female								
No	11	1.00	1.00		49	1.00	1.00	
Yes	18	1.07	1.33	0.32, 5.60	25	0.61	0.43	0.21, 0.87
Age (years)								
<50	4	1.00	1.00		3	1.00	1.00	
50–64	17	4.96	5.12	0.90, 29.21	21	10.16	7.57	2.09, 27.45
≥65	8	11.67	29.67	2.36, 373.35	50	29.47	17.97	5.09, 63.49
Lived in Japan (years)								
<10	2	1.00	1.00		59	1.00	1.00	
10–19	1	0.11	0.01	0.00, 0.67	6	1.92	1.04	0.35, 3.03
≥20	26	0.72	0.10	0.00, 3.95	9	14.39	6.96	1.69, 28.65
Smoking status								
Nonsmokers	16	1.00	1.00		32	1.00	1.00	
Former smokers	11	1.41	1.31	0.30, 5.81	34	1.73	0.81	0.39, 1.70
Current smokers	2	0.38	0.49	0.04, 6.06	8	1.40	1.04	0.36, 3.02
Drinking status								
Nondrinkers	7	1.00	1.00		23	1.00	1.00	
Former drinkers	2	0.52	1.64	0.13, 20.15	14	0.50	0.81	0.33, 1.98
Current drinkers	20	1.43	3.94	0.70, 22.52	37	0.43	0.58	0.28, 1.21
History of peptic ulcer								
No	22	1.00	1.00		67	1.00	1.00	
Yes	7	4.20	3.91	0.59, 26.11	7	1.26	0.41	0.16, 1.07
Parental history of gastric cancer								
No	26	1.00	1.00		70	1.00	1.00	
Yes	3	8.08	1.80	0.11, 29.50	4	1.58	0.68	0.20, 2.36
Helicobacter pylori infection								
No	2	1.00	1.00		20	1.00	1.00	
Yes	27	28.17	34.88	5.25, 231.66	54	11.43	9.34	5.04, 17.30

* OR, odds ratio; CI, confidence interval.
† Adjusted odds ratios obtained from a multiple logistic regression that included age (years), years lived in Japan, drinking status, smoking status, history of peptic ulcer, parental history of gastric cancer, and H. pylori infection.

area) (figure 1). Although our sample distribution is slightly shifted to higher income levels as compared with the census distribution, it is remarkably similar to that of Japanese Americans in King County. The 5-year gap between our sample and the census population might have contributed to the slightly higher income levels observed in our study sample because of the rate of inflation in household income between 1990 and 1994. Thus, it is considered that our Seattle Japanese-American sample reasonably represents the Japanese-American population in the area, although we must be cautious about possible selection bias when a comparison of health outcomes is made between populations.

One of the important questions in the study was if the rate of H. pylori infection in Japanese Americans in Seattle is different from those of other populations. Figure 2 shows that the age-specific infection rates of Japanese Americans are consistently lower than those of native Japanese in Hokkaido (38) and African Americans and European Americans in Houston, Texas (39), although caution must be taken because of differences in sampling methods and sample size among the four populations. It is interesting to observe the equivalent prevalence of H. pylori infection in African Americans and native Japanese. If H. pylori infection were a dominant factor to elevate the gastric cancer risk, mortality for gastric cancer in African
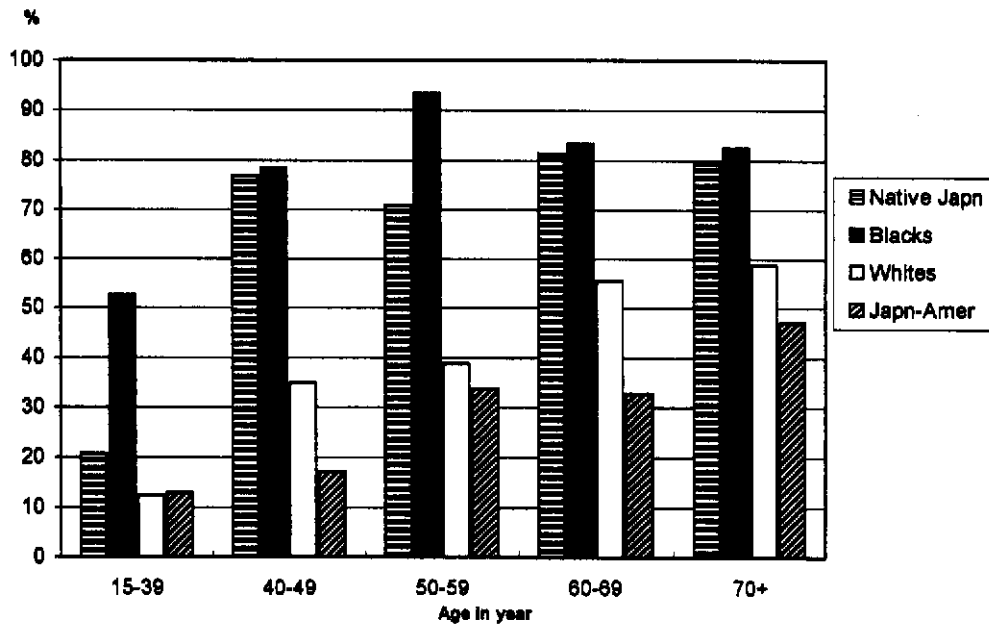
FIGURE 2. Comparison of seroprevalence of *Helicobacter pylori* infection among four populations: native Japanese (native Japn) in Japan, 1990; Blacks and Whites in Houston, Texas, 1989–1990; and Japanese Americans (Japn-Amer) in King County, Washington, 1994. Sources: for native Japanese, M. Asaka et al. Figure 2 in Gastroenterology 1992;102:760-6; for Blacks and Whites, D. Graham et al. Figure 1 in Gastroenterology 1991;100:1495-501, and additional information from D. Y. Graham.

Americans would be close to that in native Japanese. However, the actual mortality of African Americans was one fourth of that of native Japanese (9.8 vs. 40.8/100,000 persons for 1983–1987) (2), implying that other risk factors unique to Japanese may play a significant role in the etiology of gastric cancer.

Another important question was whether the prevalence of chronic atrophic gastritis in Japanese Americans in Seattle differs from that in native Japanese in Japan. The data from Seattle were compared with those from 25,415 persons in urban areas in Japan (40), as shown in figure 3. The prevalence of
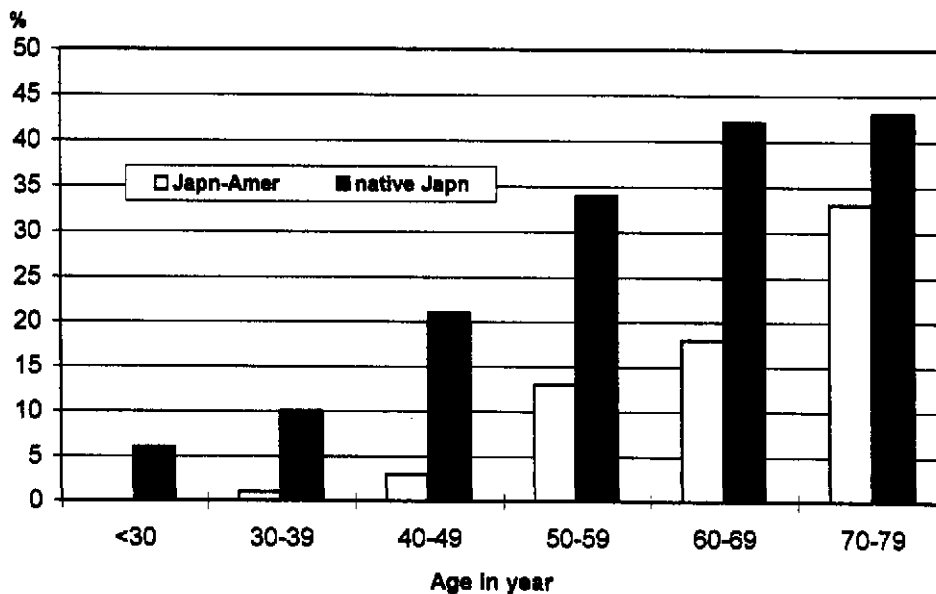
FIGURE 3. Comparison of prevalence of chronic atrophic gastritis between Japanese Americans (Japn-Amer) in Seattle, Washington, 1994, and native Japanese (native Japn) in urban areas of Japan, 1991–1995. Source: for native Japanese, K. Miki. Jpn J Electroph 1996;40:295-8.

chronic atrophic gastritis is clearly age dependent in both populations. For each age group, a higher prevalence of chronic atrophic gastritis is observed in native Japanese than in Japanese Americans, which coincides with trends in *H. pylori* prevalence compared between the two populations (figure 2). The questions on the incidence of gastric cancer in the two populations remain to be answered in the future.

The prevalence of chronic atrophic gastritis was not found to be associated with alcohol consumption, smoking status, or history of death of either parent due to gastric cancer in the present study. In a similar study conducted by Tsugane et al. (41), there was no association between alcohol consumption and chronic atrophic gastritis in Japanese men aged 40–49 years. This is consistent with the fact that there is no strong evidence that alcohol plays an etiologic role in stomach cancer (6). Smoking status was not associated with the prevalence of chronic atrophic gastritis in the present study, but Tsugane et al. (41) reported a negative association between smoking and chronic atrophic gastritis. However, a study among Japanese workers reported a dose-dependent positive association between smoking and PG I levels and the PG I/PG II ratio (42). As reviewed by the US Surgeon General (43), epidemiologic studies have shown an association between smoking and stomach cancer, although its association is weak in comparison with those found between smoking and other cancers. Tsugane et al. (41) also reported a positive association between chronic atrophic gastritis and family history of gastric cancer in either parent or any sibling, whereas no such association was found in the present study.

Unlike the second to fourth generation Japanese Americans, the first generation did not show an association between the years lived in Japan and the presence of chronic atrophic gastritis. This is possibly due to the small number of individuals ($n = 5$) in this group who lived in Japan for less than 10 years but who had a high prevalence (40 percent) of chronic atrophic gastritis, as compared with its prevalence in persons who lived in Japan for 10–19 years (7 percent) and in persons who lived there for >20 years (32.5 percent). As an increased risk for chronic atrophic gastritis was found in persons who lived in Japan for 20 years and longer among the second to fourth generation Japanese (table 6) and in both sexes (table 5), it is likely that long-term residence in Japan (or long-term exposure to the Japanese environment) is a risk factor for chronic atrophic gastritis, in addition to age and *H. pylori* infection. Possible risk factors associated with the Japanese environment include a high consumption of rice and salted foods (salted fish and pickles) (6), which had been a main source of food in rural areas in

Japan during the winter until around 1970 because of the lack of refrigeration. Most Japanese Americans who lived in Japan for many years had possibly consumed rice and salted foods every day prior to 1970 and might have continued these eating habits even after immigrating or returning to the United States. This should be clarified in a future study.

The finding that PG I levels and PG I/PG II ratios were significantly less in subjects with chronic atrophic gastritis who were *H. pylori* seronegative is interesting. Since the absolute level of PG I and PG I/PG II ratios correlates with the degree of atrophic gastritis (10), subjects with more gastric atrophy are more likely to be *H. pylori* seronegative. This is consistent with other observations that *H. pylori* do not thrive in atrophic gastric mucosa (34–36). Furthermore, since antibodies to *H. pylori* persist for several years after elimination of the bacteria, it is likely that these seronegative individuals with chronic atrophic gastritis have had atrophic mucosa for some time and perhaps are at the highest risk for cancer development.

The next phase of the study will involve upper endoscopic examination to confirm histologically the presence of intestinal metaplasia in individuals with a low PG I level and PG I/PG II ratio. Because individuals with chronic atrophic gastritis are considered to have a higher risk for gastric cancer, the endoscopic examination will also serve the purpose of screening for early tumors.

At present, screening for gastric cancer has not been recommended by either the National Cancer Institute or the American Cancer Society. However, such screening should be considered for the following reasons. 1) The pepsinogen test as a first screening of persons with chronic atrophic gastritis and endoscopy as a second screening are technically feasible (9–14, 44). 2) The estimated number of deaths due to gastric cancer in 1997 is 14,000, which is comparable to 8,300 deaths due to rectal cancer, 12,400 deaths due to liver cancer, 9,490 deaths due to skin cancer, 14,200 deaths due to ovarian cancer, or more than 4,800 deaths due to cancer of the cervix uteri and 6,000 deaths due to cancer of the corpus uteri (45). Thus, gastric cancer is not a rare disease in the United States. 3) Gastric cancer is one of the five most frequently diagnosed cancers in some ethnic populations in the United States, including Koreans, Japanese, Vietnamese, Hawaiians, Alaska natives, African Americans, Chinese, and Hispanics. Their annual average incidence rates ranged from 13.0 per 100,000 persons in Hawaiian females to 48.9 per 100,000 persons in Korean males for 1988–1992 (45). 4) The 5-year survival rate of gastric cancer in Osaka, Japan, where gastric cancer screening is conducted, is

34.1 percent (46), a much higher proportion than that in Detroit, Michigan, where its screening has not been promoted (11.3–14.5 percent depending on income levels) (47). Unlike cancers of the lung, liver, and pancreas, gastric cancers are potentially curable if they are diagnosed at early stages. Thus, the screening of gastric cancer in the United States should be available to persons who are considered to be at high risk for this disease.

REFERENCES

1. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of eighteen major cancers in 1985. Int J Cancer 1993;54: 594–606.
2. Tominaga S, Kuroishi T, Aoki K, eds. Cancer mortality statistics in 33 countries 1953–1992. Geneva, Switzerland: International Union Against Cancer, 1998:15, 47.
3. Fujimoto I, Hanai A. Trends of cancer incidence by site and histological types in Osaka, Japan, 1963–1983. Gann Monogr Cancer Res 1987;33:25–31.
4. Sipponen P, Jarvi O, Kekki M, et al. Decreased incidences of intestinal and diffuse types of gastric carcinoma in Finland during a 20-year period. Scand J Gastroenterol 1987;22: 865–71.
5. Rios-Castellanos E, Sitas F, Shepherd NA, et al. Changing pattern of gastric cancer in Oxfordshire. Gut 1992;33:1312–17.
6. Kono S, Hirohata T. A review on the epidemiology of stomach cancer. J Epidemiol 1994;4:1–11.
7. Correa P. The epidemiology of gastric cancer. World J Surg 1991;15:228–34.
8. Correa P. A human model of gastric carcinogenesis. Cancer Res 1988;48:3554–60.
9. Samloff IM, Varis K, Ihamaki T, et al. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology: a study in relatives of patients with pernicious anemia. Gastroenterology 1982;3:204–9.
10. Miki K, Ichinose M, Shimizu A, et al. Serum pepsinogens as a screening test of extensive chronic gastritis. Gastroenterol Jpn 1987;22:133–41.
11. Miki K, Ichinose M, Kawamura N, et al. The significance of low serum pepsinogen levels to detect stomach cancer associated with extensive chronic gastritis in Japanese subjects. Jpn J Cancer Res 1989;80:111–14.
12. Miki K, Ichinose M, Ishikawa K, et al. Clinical application of serum pepsinogen I and II levels for mass screening to detect gastric cancer. Jpn J Cancer Res 1993;84:1086–90.
13. Miki K, Ichinose M, Kakei N, et al. Gastric cancer screening with serum pepsinogen test "stomach dry dock." In: Health tactics in the 21st century. Proceedings of the IHEA Tokyo Conference '94. Tokyo, Japan: International Health Evaluation Association, 1994:321–5.
14. Miki K, Ichinose M, Kakei N, et al. The clinical application of the serum pepsinogen I and II levels as a mass screening method for gastric cancer. In: Takahashi K, ed. Aspartic proteinases: structure, function, biology, and biomedical implications. New York, NY: Plenum Press, 1995:139–43.
15. Warren JR. Unidentified curved *bacilli* on gastric epithelium in active chronic gastritis. (Letter). Lancet 1983;1:1273.
16. Marshall B. Unidentified curved *bacilli* on gastric epithelium in active chronic gastritis. Lancet 1983;1:1273–5.
17. Graham DY. *Campylobacter pylori* and peptic ulcer disease. Gastroenterology 1989;96:615–25.
18. Nomura A, Stemmermann GN, Chyou P, et al. *Helicobacter pylori* infection and the risk for duodenal and gastric ulceration. Ann Intern Med 1994;120:977–81.
19. Cover TL, Blaser MJ. *Helicobacter pylori*: a bacterial cause of gastritis, peptic ulcer disease, and gastric cancer. ASM News 1995;61:21–6.
20. 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;55:562–5.
21. Kuipers EJ, Perez-Perez GI, Meuwissen SGM, et al. *Helicobacter pylori* and atrophic gastritis: importance of the *cagA* status. J Natl Cancer Inst 1995;87:1777–80.
22. Kuipers EJ, Uyterlinde AM, Pena AS, et al. Long-term sequelae of *Helicobacter pylori* gastritis. Lancet 1995;345:1525–8.
23. Asaka M, Kato M, Kudo M, et al. Relationship between *Helicobacter pylori* infection, atrophic gastritis and gastric carcinoma in a Japanese population. Eur Gastroenterol Hepatol 1995;7(suppl 1):s7–10.
24. Nomura A, Stemmermann GN, Chyou PH, et al. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J Med 1991;325:1132–6.
25. Asaka M, Kimura T, Kato M, et al. Possible role of *Helicobacter pylori* infection in early gastric cancer development. Cancer 1994;73:2691–4.
26. Correa P, Fox J, Fontham E, et al. *Helicobacter pylori* and gastric carcinoma: serum antibody prevalence in populations with contrasting cancer risks. Cancer 1990;66:2569–74.
27. The Eurogast Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. Lancet 1993;341:1359–62.
28. Fukao A, Hisamichi S, Ohsato N, et al. Correlation between the prevalence of gastritis and gastric cancer in Japan. Cancer Causes Control 1993;4:17–20.
29. US Department of Commerce, Bureau of the Census. 1990 Census of population, social and economic characteristics. Washington, DC: US GPO, 1990:374. (Publication no. 1990 CP-1-49).
30. Ichinose M, Miki K, Furihata C, et al. Radioimmunoassay of serum group I and group II pepsinogens in normal controls and patients with various disorders. Clin Chim Acta 1982;126: 183–91.
31. Crabtree JE, Shalcross TM, Heatley RV, et al. Evaluation of a commercial ELISA for serodiagnosis of *Helicobacter pylori* infection. J Clin Pathol 1991;44:326–8.
32. Newell D, Stacey A. Serology. In: Northfield TC, Mendall M, Goggin PM, eds. *Helicobacter pylori* infection: pathophysiology, epidemiology and management. Boston: Kluwer Academic Publishers, 1993:139–47.
33. SPSS, Inc. SPSS/PC+ advanced statistics, version 8.0. Chicago, IL: SPSS, Inc, 1997.
34. Siurala M, Sipponen P, Kekki M. *Campylobacter pylori* in a sample of Finnish population: relations to morphology and functions of gastric mucosa. Gut 1988;29:909–15.
35. Karnes WJ, Samloff IM, Siurala M, et al. Positive serum antibody and negative tissue staining for *Helicobacter pylori* in subjects with atrophic body gastritis. Gastroenerology 1991; 101:167–74.
36. Fukuda H, Saito D, Hayashi S, et al. *Helicobacter pylori* infection, serum pepsinogen level and gastric cancer: a case-control study in Japan. Jpn J Cancer Res 1995;86:64–71.
37. Benfante R, Reed D, MacLean C, et al. Response bias in the Honolulu Heart Program. Am J Epidemiol 1989;130: 1088–100.
38. Asaka M, Kimura T, Kudo M, et al. Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic

Japanese population. Gastroenterology 1992;102:760–6.

39. Graham D, Malaty HM, Evans DG, et al. Epidemiology of *Helicobacter pylori* in an asymptomatic population in the United States: effect of age, race, and socioeconomic status. Gastroenterology 1991;100:1495–501.

40. Miki K. Evaluation of the serum pepsinogen test for gastric cancer screening. Jpn J Electroph 1996;40:295–8.

41. Tsugane S, Kabuto M, Imai H, et al. *Helicobacter pylori*, dietary factors, and atrophic gastritis in five Japanese populations with different gastric cancer mortality. Cancer Causes Control 1993;4:297–305.

42. Kikuchi S, Inaba Y, Osamu W, et al. The association of smoking and drinking habits with serum pepsinogens. Int J Epidemiol 1995;24:346–53.

43. Surgeon General of the United States. The health consequences of smoking: cancer. Rockville, MD: US Public Health Service, 1982. (Publication no. DHHS (PHS) 82-

50179).

44. Miki K, Ichinose M, Yahagi N, et al. Efficiency of gastric cancer screening system using serum pepsinogen tests. In: Siewert JR, Roder JD, eds. Progress in gastric cancer. Proceedings of the 2nd International Gastric Cancer Congress, Munich, Germany, April 27–30, 1997. Bologna, Italy: Monduzzi Editore, 1997:87–93.

45. American Cancer Society. Cancer facts & figures—1997. Atlanta, GA: American Cancer Society, Inc, 1997.

46. Hanai A, Tsukuma H, Hiyama T, et al. Cancer survival in Osaka. In: Tominaga S, Aoki K, Fujimoto I, et al, eds. Cancer mortality and morbidity statistics. Ann Arbor, MI: CRC Press, 1994:159–65.

47. Gorey KM, Holowaty EJ, Fehringer G, et al. An international comparison of cancer survival: Toronto, Ontario, and Detroit, Michigan, metropolitan areas. Am J Public Health 1997;87: 1156–63.