Overview on Gastric Cancer

Chapter 5

Helicobacter Pylori Infection and Chronic Atrophic Gastritis among Asian Immigrants in the Seattle Area, U.S.A.

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Abstract

Helicobacter pylori (*H. pylori*) is considered to play an important role in gastric carcinogenesis, since chronic atrophic gastritis, a precursor of gastric carcinoma, is caused by *H. pylori*. We previously examined the role of *H. pylori* for gastric cancer by examining the relationship between chronic atrophic gastritis and *H. pylori* infection among Japanese Americans in Seattle and found that chronic atrophic gastritis was significantly associated with age over 50 years, *H. pylori* infection, and greater than 20 year residence in Japan. In this study, we extended these observations by examining prevalence of *H. pylori* infection and chronic atrophic gastritis among Asian immigrants from China, South Korea, Philippine and Vietnam. Age-adjusted prevalence of *H. pylori* infection ranged from the lowest in Japanese immigrants (26.0%) to the highest in Vietnam immigrants (43.3%), as compared to 70.6% in rural

residents in Japan. Age-adjusted prevalence of chronic atrophic gastritis was found to be the lowest in Filipino immigrants (2.2%) and the highest in Japanese immigrants (11.6%), as compared to 34.3% in rural residents in Japan. Multiple logistic regression analysis was conducted to estimate the risk of chronic atrophic gastritis associated with other factors. It was found that having *H. pylori* infection significantly elevated the risk for chronic atrophic gastritis (5.856, $p<0.001$). At present, the screening of gastric cancer has not been recommended by either the National Cancer Institute or the American Cancer Society. However, such screening should be considered in high risk groups because the pepsinogen test to detect chronic atrophic gastritis with follow-up is technically feasible and may lead to the detection of gastric cancer in the United States.

Key words: gastric cancer; gastric cancer screening; *Helicobacter pylori*; pepsinogen; chronic atrophic gastritis; Asian American immigrants; cancer epidemiology; high risk populations for gastric cancer

Abbreviations: ELISA, enzyme-linked immunosorbent assay; *H. pylori, Helicobacter pylori*; IgG, immunoglobulins G; 95% CI, 95 percent confidence interval; PG I, pepsinogen I; PG II, pepsinogen II; the U.S., the United States of America

1. Introduction

Although gastric cancer mortality has declined over the past several decades, it is the second highest cause of male cancer deaths and 4th highest cause of female cancer deaths worldwide [1]. One of the highest rates is found in Japan (53.9 per 100,000 persons for males and 27.0 per 100,000 persons for females in 2007) and one of the lowest is present in the United States (4.6 per 100,000 persons for males and 3.2 per 100,000 persons for females in 2005) [2]. Because of Japan's high gastric cancer incidence screening program for gastric cancer has been carried out in Japan for all residents aged 40 years and over since 1983, whereas gastric cancer screening program is not practiced in the U.S. Such policy differences are responsible for better 5-year survival rates in Japan (62.1%) than in the U.S. (25.7%) [3].

Chronic atrophic gastritis precedes the development of intestinal type gastric carcinoma [4-5]. Thus, persons with chronic atrophic gastritis are considered to be at a higher risk for having or developing gastric cancer. 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 predicts the presence of atrophic gastritis [6-8]. This method has been used in Japan as a screening test to detect individuals at high risk for gastric cancer and subsequent upper endoscopic examination [9-11]. Since the first reports on gastric infection with *H. pylori* in the early 1980's [12,13], it has been established that *H. pylori* infection is strongly associated with peptic ulcer disease [14-17], and chronic atrophic gastritis and intestinal metaplasia [18-20].

H. pylori strains possessing cytotoxin associated gene A (cagA) are considered to enhance induction of acute inflammation leading to the development of atrophic gastritis and gastric cancer [18]. Early life acquisition of *H. pylori* has been considered to increase the risk of developing both gastric cancer and gastric ulcer [17]. A growing body of research suggests a link between *H. pylori* infection and gastric carcinoma [18-23]. Furthermore, ecological studies show a significant relation between the prevalence of *H. pylori* infection and gastric cancer incidence and mortality [24] and an association between prevalence of chronic atrophic gastritis and the standard mortality ratio for gastric cancer [25]. There must be additional risk factors which play an important role in the causation of gastric cancer, since only a small proportion of persons infected with *H. pylori* develop gastric carcinoma. However, *H. pylori* plays an important role in gastric carcinogenesis, since almost all gastric cancer including both intestinal type and diffuse type arise from the mucosa infected by *H. pylori,* and the results of four cohort studies suggest that *H. pylori* eradication reduces gastric cancer incidence.

Namekata et al. examined the role of *H. pylori* in gastric cancer by examining the relationship between chronic atrophic gastritis and *H. pylori* infection among Japanese Americans who share a common genetic background with native Japanese who suffer one of the highest gastric cancer mortality of all populations, but Japanese Americans live in the nation where gastric cancer mortality is the lowest in the world [26]. They found that chronic atrophic gastritis was significantly associated with age over 50 years, *H. pylori* infection, and greater than 20-year residence in Japan. This suggests that *H. pylori* infection earlier in life and other unknown exposure factors in Japan might have played an important role in the development of chronic atrophic gastritis and then gastric cancer [26].

They also observed that *H. pylori* infection rates increased from 18% for 40-49 years old to 47% for 70 years old and over among Japanese Americans (comprising of 12.9% 1st, 41.2% 2nd, 44.2% 3rd, and 1.7% 4th generations) while Asaka et al. reported that its rates among Japanese in Japan were consistently high, 70-80% after 40 years old [27]. The rates of chronic atrophic gastritis among Japanese Americans were found to be linearly increased with age from 1% for 30-39 years old to 33% for 70-79 years old, as compared with 10% for 30-39 years old to 43% for 70-79 years old among Japanese in Japan [28]. By migrating from Japan to the U.S. both the prevalence of *H. pylori* infection and the prevalence of chronic atrophic gastritis among Japanese Americans significantly decreased from the level of Japanese in Japan.

Now our question is if the prevalence of chronic atrophic gastritis is proportionate to the prevalence of *H. pylori* infection in other Asian immigrants in the U.S. To answer this question, we conducted screening and surveys among immigrants from Korea, China, Vietnam, and Philippine in the Seattle area. We also examined the association of *H. pylori* infection and chronic atrophic gastritis with possible risk factors.

2. Materials and Method

The study sample consisted of male and female Asian immigrants residing in the greater Seattle area (King County). Study participants were recruited through churches and community centers. Completed clinical and survey information was collected from a total of 298 males and 505 females in 2004-2005, as shown in **Table 1**.

Table 1: Study subjects

Immigrants	Both genders	Males	Females
Koreans	207	79	128
Chinese	223	76	147
Vietnamese	199	84	115
Filipinos	174	59	115
Total	803	298	505

The study protocol and the consent form were approved by the human subject committee at the Pacific Rim Disease Prevention Center. The consent form was translated into Korean, Chinese, Vietnamese and Filipino for those who cannot read English. Screening was conducted at churches and community centers. All subjects signed on the consent form before their participation in the study. Four drops of blood were taken from a finger of each subject and collected on a filtered paper (Eiken Chemical Co., Tokyo). The collected filters were shipped with ice packs to the Eiken Chemical Company's laboratory by overnight freight service. Temperature monitoring confirmed all specimen were kept below 25°C. *H. pylori* antibody was tested by "E plate 'Eiken' Disk *H. Pylori* Antibody" (Eiken Chemical Co., Tokyo) and pepsinogen I and II levels were measured by ELISA using "E plate 'Eiken' Disk PGI or II" (Eiken Chemical Co., Tokyo).

Subjects with chronic atrophic gastritis were defined as those with PG I $\leq$ 70 μg/liter and PG I/PG II ratio $\leq$ 3.0. Specimens having greater than 12.5 units/ml for IgG antibodies were considered to be positive for *H. pylori* infection.

The questionnaire was translated in each language of Korean, Chinese, Vietnamese and Filipino for those who cannot read English. Surveys were conducted with help from volunteers 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 non-drinkers.

Two analyses with multiple logistic regression were conducted: to predict seropositivity of *H. pylori* infection by age, alcohol consumption, smoking status, history of digestive disease, and family history of gastric cancer; and to predict the presence of chronic atrophic gastritis by

the same factors as those in analysis for *H. pylori* infection. Analyses were conducted by using SPSS 11.5 (SPSS Inc., Chicago, Illinois) [29].

3. Results

Characteristics of the study subjects are presented in **Table 2**. More women participated in the study than men: ranging from 58.1% for Vietnamese women to 67.1% for Chinese women. More young Koreans and Vietnamese participated in the study than Chinese and Filipinos. Almost all subjects were the 1st generation with few exceptions. According to median income based on zip code of subjects' residences, about 70% of Korean subjects lived in the areas with the median income of $50, 000 or more, while only 25-35% of Chinese, Vietnamese and Filipinos lived in such medium-high income area. Rates of current drinkers ranged from 25% of Koreans to 57% of Vietnamese. Current smokers were extremely few in all immigrants: 2.7% of Chinese to 9.7% of Vietnamese. Having family history of gastric cancer appeared highest in Koreans, 16.6%, and lowest in Filipinos, 5.2%. Vietnamese had highest prevalence of digestive disease, 18.7%, whereas Filipinos had lowest prevalence, 11.0%.

Table 2: Characteristics of Asian Immigrant subjects in the Seattle area

	Chinese	**Koreans**	**Vietnamese**	**Filipinos**
	n=222	n=207	n=198	n=173
	(%)	(%)	(%)	(%)
Sex: males	32.9	37.7	41.9	33.5
females	67.1	62.3	58.1	66.5
Age: ≥49	23.8	46.3	49.0	19.1
50-64	34.7	37.7	36.9	26.6
65-74	28.4	12.1	10.6	26.6
≥75	13.1	3.9	3.5	27.7
Generation: 1st	91.4	96.6	100.0	96.5
2nd	7.7	3.4		3.5
3rd	0.9	0.0		
Income: ≤$29K	13.1	1.0	3.0	4.2
$30K-$49K	52.6	30.7	71.7	60.4
$50K-$69K	21.2	60.8	24.8	32.4
≥$70K	13.1	7.5	0.5	3.0
Alcohol: non-drinkers	65.6	75.3	42.8	67.1
current drinkers	34.4	24.7	57.2	32.9
Smoking: nonsmokers	90.1	82.2	81.5	80.9
ex-smokers	7.2	11.2	8.8	14.5
current smokers	2.7	6.6	9.7	4.6
Family history of gastric cancer	12.0	16.6	6.1	5.2
Having digestive disease	16.2	14.4	18.7	11.0

Figure 1 shows age-adjusted prevalence rates of *H. pylori* infection and chronic atrophic gastritis among Asian immigrants in addition to Japanese immigrants [26] and Japanese in a rural area in Japan [30] from the previous surveys. *H. pylori* infection rates were the lowest in Japanese immigrants, 26.0%, and in Filipino immigrants, 26.3%, and the highest in Japanese in rural Japan, 70.6%. On the other hand, prevalence rates of chronic atrophic gastritis are 2.2%, the lowest in Filipino immigrants, 4.6% in Chinese immigrants, 6.3% in Vietnamese immigrants, 7.6% in Korean immigrants, 11.6 % in Japanese immigrants and 34.3%, the highest in Japanese living in rural Japan. The order of *H. pylori* infection is not the same as the order of chronic atrophic gastritis rates.

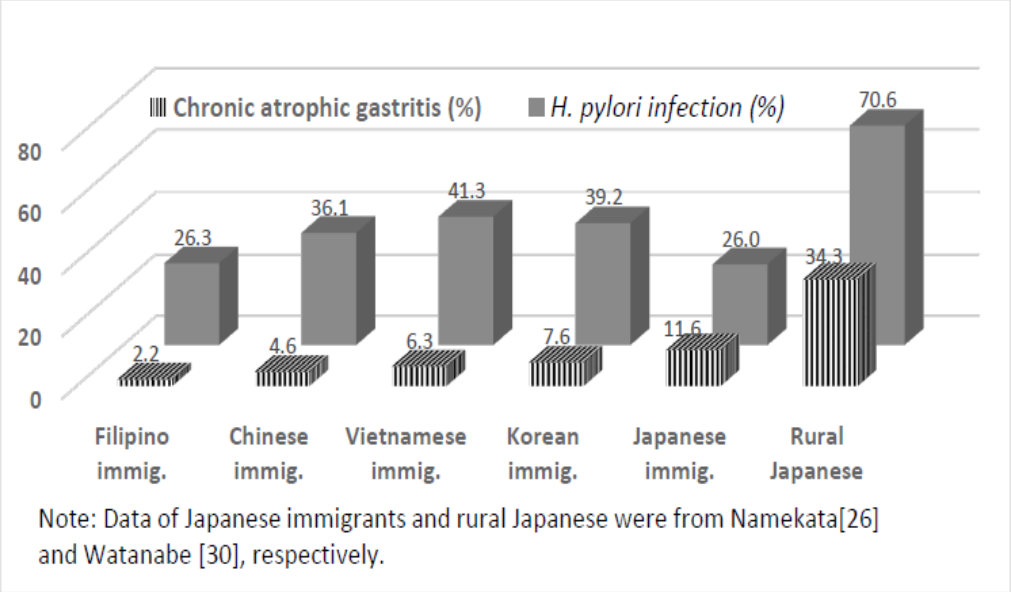

Figure 1: Age-adjusted prevalence of *H. pylori* infection and chronic atrophic gastritis among Asian immigrants in Seattle and among rural Japanese in Japan

The results of multiple logistic regression analysis to predict seropositivity of *H. pylori* with age, sex, race, drinking, smoking, having digestive disease, and family history of gastric cancer are presented in **Table 3**. Significant odds ratios were observed for being females (0.725, $p<0.05$) when setting males as a reference variable, increasing age from ≤49 years old to 65-74 years old (1.579, $p<0.05$), Vietnamese as compared to Chinese (1.615, $p<0.05$), family history of gastric cancer (1.658, $p<0.01$), and drinking habit (0.696, $p<0.05$).

Table 4 presents the results of multiple logistic regression analysis to predict the presence of chronic atrophic gastritis. The odds ratio of chronic atrophic gastritis among women was one-third lower than among men (0.326, $p<0.001$). Odds ratios for persons 65-74 years old and 75 years old and over were significantly and marginally higher (2.441, $p<0.05$ and 2.177, $p<0.10$, respectively), as compared with that for persons younger than 50 years old. When making Chinese as a reference group, only the odds ratio for Vietnamese was significant (2.472, $p<0.017$) and those for Koreans and Filipinos were not significant. Having family history of gastric cancer and having digestive disease showed an increased risk for chronic

atrophic gastritis (7.914, p<0.001 and 6.193, p<0.001, respectively). Having *H. pylori* infection significantly elevated the risk for chronic atrophic gastritis (5.856, p<0.001). Current drinking habit and current or past smoking habits were significantly and negatively associated with chronic atrophic gastritis (0.204, p<0.001 and 0.071, p<0.001, respectively).

Table 3: Adjusted odds ratios for *H. pylori* infection in four immigrant groups combined in Seattle

Explanatory variables	Odds ratio	95% CI	P-value	
Sex				
Males	1.000			
Females	0.725	0.527-0.997	0.048	*
Age in year				
≤49	1.000			
50-64	1.057	0.741-1.507	0.759	
65-74	1.579	1.019-2.449	0.041	*
≥75	1.113	0.652-1.901	0.694	
Race				
Chinese	1.000			
Vietnamese	1.615	1.065-2.447	0.024	*
Koreans	1.246	0.819-1.894	0.304	
Filipinos	0.767	0.494-1.173	0.217	
Family history of gastric cancer				
No	1.000			
Yes	1.658	1.127-2.440	0.010	**
Having digestive disease				
No	1.000			
Yes	0.853	0.583-1.247	0.412	
Drinking habit				
No	1.000			
Yes	0.696	0.513-0.943	0.019	*
Smoking habit				
No	1.000			
Yes (current & ex-smokers)	0.856	0.643-1.141	0.290	

Note: Significance level indicates * p <0.05 and ** p <0.01.

Table 4: Adjusted odds ratios for chronic atrophic gastritis in four immigrant groups combined in Seattle

Explanatory variables	Odds ratio	95% CI	P-value	
Sex				
Males	1.000			
Females	0.326	0.189-0.561	0.000	***
Age in year				
≤49	1.000			
50-64	1.067	0.546-2.083	0.850	
65-74	2.441	1.167-5.108	0.018	*
≥75	2.177	0.884-5.361	0.090	
Race				
Chinese	1.000			
Vietnamese	2.472	1.174-5.204	0.017	*
Koreans	1.151	0.553-2.397	0.706	
Filipinos	1.158	0.512-2.618	0.724	
Family history of gastric cancer				
No	1.000			
Yes	7.914	4.466-14.023	0.000	***
Having digestive disease				
No	1.000			
Yes	6.193	3.481-11.018	0.000	***
H. pylori infection				
No	1.000			
Yes	5.856	3.318-10.336	0.000	***
Drinking habit				
No	1.000			
Yes	0.204	0.109-0.380	0.000	***
Smoking habit				
No	1.000			
Yes (current & ex-smokers)	0.071	0.021-0.248	0.000	***

Note: Significance level indicates * <0.05, ** <0.01, and *** <0.001.

4. Discussion

One of the important questions in the study was if the rates of *H. pylori* infection and those of chronic atrophic gastritis among the four Asian immigrant groups in Seattle are different from those of Japanese Americans in Seattle and of Japanese in Japan. **Figure 1** compares age-adjusted rates of *H. pylori* infection and those of chronic atrophic gastritis among the four Asian immigrant groups from the present study, Japanese immigrant group in Seattle and rural Japanese group in Kyoto Prefecture of Japan from our previous studies [26,30]. There

is no linear relationship between *H. pylori* infection rates and chronic atrophic gastritis rates: *H. pylori* infection rate of Japanese Americans was lowest (26.0%) but their chronic atrophic gastritis rate was the second highest among the six population groups and both rates of Japanese in Kyoto Prefecture were highest, 70.6% for *H. pylori* and 34.3% for chronic atrophic gastritis. This implies that other risk factors which are unique to Japanese may play a significant role in etiology of gastric cancer.

Based on adjusted odds ratios in Table 4, the risk for chronic atrophic gastritis is reduced to nearly 70% as being females, to 80% as being drinkers and to 93% as being smokers or ex-smokers. On the other hand, the risk for chronic atrophic gastritis is increased to 2.4 times among seniors as compared with persons younger than 50 years old, to 2.5 times among Vietnamese immigrants as compared with Chinese immigrants, to 7.9 times for persons with family history of gastric cancer, to 6.2 times for persons having digestive disease, and to 5.9 times for persons infected with *H. pylori*. In the similar study conducted by Tsugane et al., there was no association between alcohol consumption and chronic atrophic gastritis in Japanese men aged 40 to 49 years [31]. Although there has been no strong evidence that alcohol plays an etiological role in gastric cancer [32], our results imply that drinking habits among Asian immigrants might prevent persons from developing chronic atrophic gastritis.

With regard to smoking status, our result is consistent with Tsugane et al. [31] reporting a negative association between smoking and chronic atrophic gastritis. However, a study among Japanese workers reported a dose-dependent positive association between smoking and PGI levels and PGI/PGII ratio [33]. As reviewed by the U.S. Surgeon General [34] epidemiological 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. Also, our result supports the findings by Tsugane et al. showing a positive association between chronic atrophic gastritis and family history of gastric cancer in either parent or any sibling [31].

At present, the gastric cancer screening has not been recommended by either the National Cancer Institute or the American Cancer Society. However, such screening should be considered in high risk groups for the following reasons: (i) The serum pepsinogen test as a first screening of persons with chronic atrophic gastritis and endoscopy as a secondary screening are technically feasible [6-11,35]; (ii) Estimated deaths due to gastric cancer in 2019 in the U.S. is 11,140, which is comparable to 13,980 deaths due to ovarian cancer, 4,250 deaths due to uterine cervix cancer and 12,160 deaths due to uterine corpus cancer [36]. Thus, gastric cancer is not a rare disease in the U.S.; (iii) Gastric cancer is one of the five most frequently diagnosed cancers in some ethnic populations in the U.S. including Koreans, Japanese, Vietnamese, Hawaiians, Alaska natives, African Americans, Chinese and Hispanics. The average incidence rates in men ranged from 15.3 per 100,000 in Hispanics to 48.9 per 100,000 in Koreans for 1988-92

[37]; (iv) The five year survival rates of gastric cancer in Japan, where gastric cancer screening has been conducted, is 60.3 percent for both genders combined, a much higher proportion than that in the U.S., where its screening has not been promoted (33.1 percent for both genders combined) [38]. 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 U.S. should be considered for persons at high risk for this disease including Asian immigrants, Hawaiians, Alaska natives, African Americans, and Hispanics.

Since gastric cancer prevention screening has been conducted in Japan, it is recommended to adopt their method and criteria in the U.S. as well as in other countries. Screening participants are classified according to the results of the two serologic tests, anti-*Hp* IgG antibody titers and the PG I and II levels: Group A [*Hp*(-)PG(-)], infection free subjects who are not required for endoscopic follow-up examinations; Group B [*Hp*(+)PG(-)], chronic atrophic gastritis free or mild who are required to eradicate *H. pylori*; Group C [*Hp*(+)PG(+)], chronic atrophic gastritis who are required to eradicate *H. pylori* and to have continuous endoscopic follow-up examinations and ; Group D [*Hp*(-)PG(+)], severe chronic atrophic gastritis with extensive intestinal metaplasia who are required for continuous endoscopic follow-up examinations [39].

5. Note

Parts of this work were presented at the following meetings:

- The 67th Annual Meeting of American College of Gastroenterology in Seattle, Washington, October 20-22, 2002
- Digestive Disease Week Japan 2005, Kobe, Japan, October 5-8, 2005.
- Congress of Epidemiology 2006, Seattle, Washington, June 21-24,2006.

6. Acknowledgement

This work was partially supported by a Grant-in-Aid for Scientific Research (B) (No. 16406024), the Ministry of Education, Science, Sports and Culture of Japan. The Collaboration and technical assistance from Eiken Chemical Company is greatly appreciated in providing screening of *Helicobacter pylori* infection and chronic atrophic gastritis. Dr. Michael B. Kimmey of Franciscan Digestive Care Associates provided invaluable comments on the draft of the manuscript. We express our sincere appreciations to the following organizations for their cooperation and support in conducting screening and survey: Kawabe Memorial House, Chinese Baptist Church, Southern Chinese Baptist Church, Korean United Presbyterian Church, Korean Presbyterian Church of Seattle, Vietnam Catholic Church, Refugee Women's Alliance (ReWA), Southern Asian Outreach Program and Filipino Community Center. Lastly,

we are indebted to many volunteers for their time and assistance in conducting the screening.

7. References

1. Garcia M, Jemal A, Ward EM, Center MM, Hao Y, Siegel RL, Thun MJ. Global Cancer Facts & Figures 2007. Atlanta, GA: American Cancer Society, 2007.

2. Health and Welfare Statistics Association. Kokumin-eisei no dokou (Trends in Nation's Health). Kosei no shihyou (Index of Health and Welfare) 2009; 56(9): 424-425.

3. National Cancer Center. Cancer Statistics in Japan 2008. Table 20. International comparison of cancer survival rates. p. 46, 2010.

4. Correa P. The epidemiology of gastric cancer. World J. Surg. 1991;15:228-34.

5. Correa P. A human model of gastric carcinogenesis. Cancer Research. 1988;48:3554-60.

6. 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;3:204-209.

7. Miki K, Ichinose M, and Shimizu A, et al. Serum pepsinogens as a screening test of extensive chronic gastritis. Gastroenterol Jpn 1987; 22(2):133-41.

8. 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;80:111-114.

9. 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.

10. 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 IHEA Tokyo Conference '94; 1994, p. 321-5.

11. 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. Aspartic Proteinases: Structure, Function, Biology, and Biomedical Implications. In: Takahashi K, eds. New York: Plenum Press, 1995:139-43.

12. Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;i:1273.

13. Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;i:1273-1275.

14. Graham DY. *Campylobacter pylori* and peptic ulcer disease. Gastroenterology 1989; 96:615-25.

15. Nomura A, Stemmermann GN, Chyou P, et al. *Helicobacter pylori* infection and the risk for duodenal and gastric ulceration. Annals of Internal Medicine 1994;120(12):977-981.

16. Cover TL, Blaser MJ. *Helicobacter pylori*: A bacterial cause of gastritis, peptic ulcer disease, and gastric cancer. ASM News 1995;61(1):21-26.

17. Blaser MJ, Chyou PH, Nomura A. Age at establishment of *Helicobacter pylori* infection and gastric carcinoma, gastric ulcer, and duodenal ulcer risk. Cancer Research 1995; 55:562-65.

18. Kuipers EJ, Perez-Perez GI, Meuwissen SGM, Blaser M. *Helicobacter pylori* and atrophic gastritis: importance of the cagA status. J Nat Cancer Inst 1995;87(23): 1777-1780.

19. Ikeda F, Shikata K, Hata J, et al. Combination of *Helicobacter pylori* antibody and serum pepsinogen as a good predictive tool of gastric cancer incidence: 20-year prospective data from the Hisayama Study. J Epidemiol 2016; JE20150258-1:1-8.

20. Taniyama Y, Katanoda K, Charvat H, et al. Estimation of lifetime cumulative incidence and mortality risk of gastric cancer. Japanese J Clinical Oncology 2017; 47(11): 1097-1102.

21. Nomura A, Stemmermann GN, Chyou PH, et al. *Helicobacter pylori* infection and gastric carcinoma among Japanese Americans in Hawaii. N Engl J of Med 1991;325(16):1132-1136.

22. Asaka M, Kimura T, Kato M, et al. Possible role of *Helicobacter pylori* infection in early gastric cancer development. Cancer 1994;73(11):2691-2694.

23. 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: 2569-2574.

24. The Eurogast Study Group. An international association between *Helicobacter pylori* infection and gastric cancer. Lancet 1993; 341:1359-1362.

25. Fukao A, Hisamichi S, Ohsato N, et al. Correlation between the prevalence of gastritis and gastric cancer in Japan. Cancer Causes and Control 1993; 4:17-20.

26. Namekata T, Miki K, Kimmey M, et al. Chronic atrophic gastritis and *Helicobacter pylori* infection among Japanese Americans in Seattle. Am J Epidemiol 2000; 151:820-830.

27. Asaka M, Kimura T, Kudo M, et al. Relationship of *Helicobacter pylori* to serum pepsinogens in an asymptomatic Japanese population. Gastroenterology 1992; 102:760-766.

28. Miki K. Evaluation of the serum pepsinogen test for gastric cancer screening. Japan J Electroph 1996; 40:295-298.

29. SPSS Inc. SPSS 16 for MS Windows, Chicago, Illinois, 2008.

30. Watanabe Y, Kurata J.H, Mizuno S,et al. *Helicobacter pylori* Infection and Gastric Cancer: A Nested Case-Control Study in a Rural Area of Japan. Digest Dis Sci 1997; 42:1383-1387.

31. 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 and Control 1993; 4:297-305.

32. Kono S, Hirohata T. A review on the epidemiology of stomach cancer. J Epidemiol. 1994; 4:1-11.

33. Kikuchi S, Inaba Y, Osamu W, et al. The association of smoking and drinking habits with serum pepsinogens. Int J Epid 1995; 24(2):346-53.

34. Surgeon General of the United States. The Health Consequences of Smoking: Cancer. Rockville, United States Public Health Service, Pub. No. DHHS (PHS) 82-50179, 1982.

35. Miki K, Ichinose M, Yahagi N, et al. Efficiency of gastric cancer screening system using serum pepsinogen test. Progress in Gastric Cancer (eds. Siewert JR, Roder JD). Proceedings of the 2nd International Gastric Cancer Congress, Munich, Germany, April 27-30, 1997.

36. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA: A Cancer J Clinician 2019; 69(1): 7-34.

37. Parker SL, Davis KJ, Wingo PA, et al. Cancer statistics by race and ethnicity. CA: A Cancer J Clinicians 1998; 48(1): 31-48.

38. Allemani C, Matsuda T, Carlo VD, et al. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 3,751,3025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet 2018; 391(10125): 1023-1075.

39. Miki K. Gastric cancer screening by combined assay for serum anti-*Helicobacter pylori* IgG antibody and serum pepsinogen levels – "ABC method". Proc. Jpn. Acad., Ser. B 2011; 87: 405-414.