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Gastric Cancer among the Japanese in Hawaii

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The incidence rate of gastric cancer among men of Japanese ancestry living in Hawaii is about one-third as high as that of their counterparts living in Japan. Because of this difference, a prospective study was conducted to identify factors related to the development of gastric cancer in Hawaii. Eight thousand and six (8,006) men born from 1900–1919 were examined from 1965 to 1968 and followed for over 25 years. During this time, 250 incident cases of gastric cancer were identified. The study has found the following: 1) prior infection with *Helicobacter pylori* bacteria increased the risk for stomach cancer; 2) cigarette smoking was positively associated with gastric cancer with age at which smoking started being an important risk factor; 3) after taking cigarette smoking into account, alcohol intake was not related to stomach cancer risk; 4) a low pepsinogen I level identified subjects at increased risk for the intestinal histologic type of gastric cancer; 5) a low serum ferritin level was a marker for increased risk of stomach cancer; 6) there was a weak indication that the intake of vegetables and fruits was inversely related to gastric cancer; 7) there was no association of stomach cancer with levels of serum cholesterol, serum uric acid, serum micronutrients (retinol, β-carotene or α-tocopherol) or blood hematocrit; 8) there was also no association of gastric cancer with body mass index or physical activity.

Key words: Gastric cancer — Hawaii — Prospective study

It has been known for many years that people of Japanese ancestry living in Hawaii, USA, have a lower risk of gastric cancer compared with people living in Japan.[1)] Recently, it was reported that the annual 1983–1987 gastric cancer incidence per 100,000 Japanese residents in Hawaii was 24.3 for men and 11.1 for women, compared with the annual 1983–1987 incidence in Miyagi, Japan of 85.4 for men and 36.7 for women.[2)]

Because of these differences, a long-term prospective project was begun over 25 years ago among Japanese men in Hawaii in an attempt to identify factors related to the occurrence of stomach cancer.

We report here the results of a series of studies undertaken to determine the association of gastric cancer with alcohol intake, cigarette smoking history, body mass index, physical activity, hematocrit levels, serum uric acid, serum cholesterol, *Helicobacter pylori* antibody status, serum ferritin, serum transferrin, serum pepsinogen I, serum micronutrient levels, and the intake of vegetables and fruits.

MATERIALS AND METHODS

Study population The subjects for this study were men of Japanese ancestry, born between 1900 and 1919, and residing on the Hawaiian island of Oahu. They were first identified by the Honolulu Heart Program in 1965.[3)] Of 11,148 eligible men, 8,006 (72%) were interviewed and examined from 1965 to 1968, 180 (2%) died before they could be examined, and 2,962 (26%) did not participate in the program. The data collected on the interviewed men included cigarette smoking history, history of alcohol use, a 24-h diet recall questionnaire, body mass index (weight in kilograms divided by the square of the height in meters), and the physical activity index (based on the weighted sum of the usual amount of time the subject spent per 24 h in different types of activity).[4)] Hematocrit levels of all subjects were determined, based on the method of Guest and Siler[5)]; serum cholesterol values (non fasting) were determined by the Auto Analyzer N-24A method[6)]; and the serum uric acid assay (non fasting) was done by the Auto Analyzer N-13B method using a phosphotungstic acid reagent.[7)]

A total of 7,498 (94%) of the men returned for a second examination between 1967 and 1970, at which time a serum specimen was obtained. Blood samples from a random sample of 20% of the men were sent to the U.S. Public Health Service Hospital in San Francisco, while samples from the remaining 5,924 men were stored at $-20^{\circ}C$ at the study site. These serum samples were used in conducting nested case-control studies measuring levels of ferritin, transferrin, IgG antibodies to *Helicobacter pylori* and pepsinogen I in the serum.

Six thousand eight hundred and sixty (6,860; 91%) of the 7,498 second exam men returned for a third round of examinations from 1971 to 1975, at which time another

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non fasting venous sample was obtained. These sera were used in conducting case-cohort studies measuring micronutrient levels of β-carotene, retinol, and α-tocopherol in the serum.

Surveillance Surveillance of the 8,006 examined men to identify incident cases of stomach cancer was accomplished by continuous review of discharge records of all general hospitals on Oahu. To reduce the possibility of missing incident cases, a computer linkage file was established with the Hawaii Tumor Registry, a member of the Surveillance, Epidemiology and End Results Program of the National Cancer Institute. Based on a 19-year follow-up survey of the study subjects since their examination in 1965 to 1968, only 1.3% of the men could not be located on Oahu. As a result, the surveillance for incident cases of stomach cancer should have been nearly complete.

There were 250 incident cases of gastric carcinoma diagnosed from 1968 to 1994 and confirmed as adenocarcinoma by examination of tissue obtained by surgery or biopsy. Eighteen cases were also clinically diagnosed but without tissue confirmation of adenocarcinoma, so they were excluded from the study. There were 16 prevalent cases of stomach cancer who had already been diagnosed at the time of their initial examination, so they were also removed from the study. As a result, 7,972 men remained in the investigation. The histological type of stomach cancer was determined according to the classification of Lauren.[8] For purposes of presentation, the intestinal-mixed-other type will be referred to as the intestinal type, which is separate from the diffuse type.

Selection of control subjects There were three types of study design used in this investigation. First, there were cohort studies involving all study subjects. The noncases who were not diagnosed with stomach cancer served as the comparison group or controls. These studies focused on cigarette smoking history, history of alcohol use, body mass index, physical activity index, hematocrit, serum uric acid and serum cholesterol levels.

Next, there were nested case-control studies using the second exam serum (1967–1970). Each case was matched to one control subject from the study cohort, according to age at examination and data of serum collection. Each control was alive at the time of the diagnosis of the matched case, so death was not a competing factor. These studies included measurements for serum ferritin, transferrin, and IgG antibodies to *H. pylori*. The number of gastric cancer cases in these nested case-control studies differed because they covered varying periods in time.

Lastly, a case-cohort study design was used for the serum obtained at the third round of examination (1971–1975). The controls were stratified by age and randomly selected from the examined men who were not incident cases of cancer. This provided a more efficient study design because other cancers were included in the original study.[9] These studies included measurements for serum β-carotene, retinol, and α-tocopherol. A similar design was used in the case-cohort study of serum pepsinogen I using second exam serum and in the case-cohort study of diet, based on the 24-h diet recall questionnaire administered during the initial exam.

Serologic methods The Allegro ferritin immunoassay system was used to measure serum ferritin levels based on the method developed by Addison *et al.*[10] Serum transferrin was measured with the Beckman immunochemistry system using the rate nephelometry method. The presence of serum IgG antibodies to *H. pylori* was determined by enzyme-linked immunosorbent assay (ELISA) with the Pyloristat kit (Whittaker Bioproducts, Walkersville, MD), as previously described.[11] Serum pepsinogen I was measured by a competitive binding double antibody radioimmunoassay method.[12] The assay of serum levels of β-carotene, retinol and α-tocopherol was performed by normal-phase high-pressure liquid chromatography on columns of Lichrosorb Si 60, as previously described.[9]

Statistical analysis Age-specific incidence rates were calculated by allocating follow-up time and incident cases of gastric cancer to the appropriate age interval. Age-adjusted means of specific variables were calculated for gastric cancer cases and noncases. Adjustment for age was done using one-way unbalanced analysis of covariance,[13] with age at the baseline examination treated as the continuous covariate. The relative risks and corresponding 95% confidence intervals for gastric cancer associated with cigarette smoking, alcohol, vegetable, and fruit intake were estimated by using the proportional hazards regression models,[14] with adjustment for relevant covariates. Estimates of the odds ratios for gastric cancer according to levels of *H. pylori* antibody, ferritin, and transferrin were obtained from the conditional logistic regression models.[15] For the study of pepsinogen I and specific serum micronutrients, including β-carotene, retinol and α-tocopherol, the odds ratios were obtained by using the unconditional logistic regression models.[16] In addition, the dose-response trend in risk for gastric cancer with increasing level for these specific variables was evaluated by means of the likelihood ratio test ($P \leq 0.05$ was considered as statistically significant).

RESULTS

The 7,972 cohort men in the study were followed for 26 years which resulted in 177,080 person-years of observation after deaths were taken into account. In all, there were 250 incident cases of stomach cancer in the cohort. The age-specific incidence rates per 100,000 person-years

Table I. Age-specific Gastric Cancer Incidence Rates per 100,000 Person-Years by Histological Type

Age at diagnosis of cancer (yr)	Person-years	Intestinal type	Diffuse type	All types
45–54	19,182	10.4 (2)[a]	5.2 (1)	15.6 (3)
55–64	59,158	50.7 (30)	20.3 (12)	74.4 (44)
65–74	67,091	143.1 (96)	34.3 (23)	183.3 (123)
75–84	28,502	157.9 (45)	59.6 (17)	252.6 (72)
85+	3,147	222.4 (7)	0 (0)	254.2 (8)

a) Number of cases in parenthesis.
The histologic type of 17 cases was not determined.

Table II. Comparison of Age-adjusted Means between Cases and Noncases for Specific Variables

Variable	Cases[a] (±1SD)	Noncases[b] (±1SD)	*P*-value
Cigarette smoking (pack-years)	28.4±1.6	23.8±0.3	0.004
Alcohol (oz/month)	16.7±1.6	13.6±0.3	0.054
Body mass index (kg/m^2)	23.6±0.2	23.9±0.04	0.188
Physical activity index	33.3±0.3	32.8±0.1	0.112
Hematocrit (%)	44.5±0.2	44.7±0.03	0.288
Serum uric acid (mg/dl)	5.9±0.1	6.0±0.02	0.359
Serum cholesterol (mg/dl)	214.9±2.4	218.5±0.4	0.145

a) The number of cases ranged from 243 to 250 for each variable, depending on the number with missing data.
b) The number of noncases ranged from 7591 to 7717 for each variable, depending on the number with missing data.

Table III. Relative Risks[a] and 95% Confidence Intervals for Gastric Cancer by Cigarette Smoking History

Cigarette history	No. of cases	No. of noncases	Relative risk	95% Confidence interval
Cigarette smoking				
Never	53	2347	1.0	
Past	49	2036	1.1	0.7–1.6
Current	148	3338	2.3	1.7–3.2
Age started smoking for current smokers				
Never	53	2347	1.0	
21+	46	1182	1.9	1.3–2.9
18–20	57	1169	2.5	1.7–3.7
≤17	44	973	2.6	1.7–3.9
			P-value for trend <0.0001	

a) Adjusted for age and alcohol intake (oz/month).

at risk by histologic type are presented in Table I. As expected, there was an increase in risk with age. There were 180 intestinal cases, 53 diffuse cases, and the histologic type of 17 cases was not determined.

Table II compares the age-adjusted means between cases and noncases for the seven listed variables. Cases had more pack-years of cigarette smoking ($P=0.004$) and more alcohol intake ($P=0.054$) than noncases, but differences in body mass index, physical activity index, hematocrit, serum uric acid, and serum cholesterol between the two groups were not remarkable.

Current cigarette smokers had an increased risk for gastric cancer in comparison with never or past smokers, as shown in Table III. When the current smokers were separated by pack-years of smoking, there was no indication that the risk progressively increased with greater exposure. The relative risks were 2.2 for less than 30 pack-years of smoking, 2.5 for 30–44 pack-years of smoking and 2.2 for 45 or more pack-years of smoking. However, there was a linear trend according to age at which the current smokers began smoking (Table III). Those who had started smoking at age 17 or younger had a 37% greater risk of stomach cancer than those who had started at age 21 or older. Pearson's correlation coefficient was −0.35 between age at which smoking started and pack-years of smoking among current smokers.

There was no association of alcohol intake with stomach cancer after adjustment for age and cigarette smoking status. The results are presented in Table IV.

In the nested case-control investigation of prior infection with *Helicobacter pylori*, there was a strong positive association between gastric cancer and the presence of *H. pylori*-specific IgG antibody. Ninety-four per cent of the gastric cancer cases (103 of 109) and 76% of the controls (83 of 109) had a positive test which resulted in an odds ratio of 6.0 (95% confidence interval, 2.1–17.3). When the cases were separated into intestinal and diffuse histological types, the association was present for both histologic types ($P<0.01$ and $P<0.05$, respectively; data not shown).

When the patients with gastric cancer and positive antibody tests were separated into tertile groupings, based on the distribution of antibody levels among control subjects, there was a significant linear trend in their odds ratios. This is shown in Table V. The 83 cases who were diagnosed 10 or more years after examination had an odds ratio of gastric cancer of 10.5 (95% confidence interval, 2.5 to 44.8; data not shown).

Table IV. Relative Risks[a] and 95% Confidence Intervals for Gastric Cancer by Alcohol Intake History

Alcohol history (oz/month)	No. of cases	No. of noncases	Relative risk	95% Confidence interval
Non drinker	86	2388	1.0	
<5	43	1626	0.9	0.6–1.3
5–14	41	1135	1.1	0.8–1.6
15–39	39	1120	1.0	0.7–1.5
40+	36	891	1.2	0.8–1.8
			P-value for trend = 0.20	

a) Adjusted for age and cigarette smoking history.

Table V. Odds Ratios for Gastric Cancer, According to *H. pylori* Test Results and Antibody Levels

H. pylori test results	No. of cases	No. of controls	Odds ratio	95% Confidence interval
Negative	6	26	1.0	
Positive				
Antibody levels				
1.00–1.70	28	27	4.7	1.5–14.4
1.71–2.20	32	28	6.3	1.9–21.0
≥2.21	43	28	7.6	2.4–23.0
			P-value for trend <0.0001	

Table VI. Odds Ratios and 95% Confidence Intervals for Gastric Cancer by Tertile Distribution of Serum Ferritin and Transferrin Levels

Serum test	No. of cases	No. of controls	Odds ratio	95% Confidence interval
Ferritin (ln ng/ml)				
<5.4	26	15	1.0	
5.4–<6.0	12	15	0.5	0.2–1.3
6.0+	8	16	0.2	0.1–0.8
			P-value for trend = 0.02	
Transferrin (mg/dl)				
<235	18	16	1.0	
235–269	15	14	1.0	0.4–2.3
270+	13	16	0.7	0.3–1.9
			P-value for trend = 0.55	

Table VI gives the odds ratios of gastric cancer by tertiles of serum ferritin and transferrin levels. There was a significant inverse trend for serum ferritin with subjects in the highest tertile having an odds ratio of 0.2, but no association was present for serum transferrin.

Next, a comparison of gastric cancer cases and controls by serum pepsinogen I levels and histologic type was done, as shown in Table VII. A low pepsinogen I level was strongly related to intestinal gastric cancer risk, resulting in an odds ratio of 9.7. A low pepsinogen I level was mainly found in the cases diagnosed with stage 3 or 4 disease (18 of 53) and not in cases diagnosed with stage 1 or 2 disease (1 of 13). No association was present for the diffuse histological type of gastric cancer.

Based on the 24-h diet recall questionnaire, a case-cohort analysis was done. Of the many nutrients and food groups included in the study, a significant inverse association was found only for vegetables and fruits, as presented in Table VIII. Subjects who were heavy consumers of vegetables and fruits had a low risk for gastric cancer.

Table VII. Comparison of Gastric Cancer Cases and Controls by Serum Pepsinogen I and Histologic Type

Pepsinogen I (ng/ml)	No. of cases	No. of controls	Odds ratio[a]	95% Confidence interval
Intestinal				
≥20	47	240	1.0	
<20	19	10	9.7	4.0–24.1
Diffuse				
≥20	18	240	1.0	
<20	1	10	1.3	0.2–11.2

a) Adjusted for age.

Table VIII. Age-adjusted Odds Ratios for Gastric Cancer by Level of Intake of Vegetables and Fruits

Intake (g/day)	No. of cases	No. of controls	Odds ratio	95% Confidence interval
Vegetables				
None	38	107	1.0	
<40	27	61	1.2	0.7–1.9
40–79	20	61	0.9	0.5–1.6
80+	26	132	0.6	0.3–0.9
			P-value for trend <0.001	
Fruits				
None	37	96	1.0	
≤150	29	84	0.9	0.6–1.5
151–300	23	80	0.8	0.5–1.3
301+	22	101	0.6	0.4–1.0
			P-value for trend = 0.05	

Table IX. Age-adjusted Odds Ratios for Gastric Cancer by Serum Vitamin Levels

Serum vitamins	No. of cases	No. of controls	Odds ratio	95% Confidence interval
β-Carotene (μg/dl)				
≤22	34	99	1.0	
23–40	23	101	0.6	0.3–1.1
41+	13	102	0.3	0.2–0.7
			P-value for trend = 0.08	
Retinol (μg/dl)				
≤55	23	100	1.0	
56–66	20	101	0.9	0.5–1.7
67+	27	101	1.2	0.6–2.2
			P-value for trend = 1.00	
α-Tocopherol (μg/ml)				
≤10.75	23	103	1.0	
10.76–13.99	20	98	0.9	0.5–1.7
14.00+	27	101	1.2	0.7–2.3
			P-value for trend = 0.45	

Table IX gives the age-adjusted odds ratios for gastric cancer by serum β-carotene, retinol and α-tocopherol levels. There was a suggestion of an inverse trend for β-carotene, but the association was not statistically significant. When the cases were separated by time interval from exam to diagnosis, the inverse association was mainly present for patients diagnosed within five years of exam ($P=0.001$), but not for patients diagnosed later ($P=0.71$)(data not shown).

DISCUSSION

A major advantage in this prospective study is that the data on exposures were obtained before the study participants were diagnosed with gastric cancer. This greatly reduced the possibility that the presence of the cancer affected the associations found in this investigation.

A prior infection with *H. pylori* bacteria had the strongest effect on increasing stomach cancer risk. Participants who had a positive IgG antibody test for *H. pylori* had a six-fold greater risk than those who had a negative test. The association was present for cases with either intestinal or diffuse gastric cancer. Increase in the antibody levels further accentuated the risk. The positive association was still present for patients whose cancer was diagnosed 10 or more years after entry into the study. Other studies have reported similar findings.[17–19]

It is now accepted that *H. pylori* causes chronic diffuse superficial gastritis.[20] This gastritis may progress to chronic atrophic gastritis[21, 22] which has been shown to be a precursor lesion of gastric carcinoma.[23, 24] Thus, it is plausible that *H. pylori* is a cause of chronic atrophic gastritis that predisposes patients to develop gastric carcinoma.

Current cigarette smokers had an elevated risk for stomach cancer. Age at which smoking started had a more important effect on gastric cancer risk than total pack-years of cigarette smoking. Past smokers, in turn had a stomach cancer rate that was not significantly different from that of never smokers.

A number of studies have also found that cigarette smokers had an elevated gastric cancer risk that was not related to the amount of cigarettes smoked.[25–28] However, several case-control studies have reported a modest dose-response association between cigarette smoking and stomach cancer.[29–31] Only one earlier study examined age at which smoking started and found that those who started before 20 years old had almost a four-fold greater risk for gastric cancer than non smokers.[29] These results are balanced by other case-control studies that have found no association with cigarette smoking.[32–34]

There was a weak indication in the data that alcohol intake increased gastric cancer risk. However, when the correlation between cigarette smoking and alcohol was taken into account, the association with alcohol intake did not persist. Several case-control studies have observed that alcohol drinkers had an increased risk for stomach cancer.[26, 28, 30, 33] The magnitude of the risk was usually less than 2, and a dose-response relation was either not found or not reported. Other case-control studies did not find any association.[31, 32, 34–37] A prospective study also did not find any relation between alcohol and gastric cancer.[38] Thus far, the weight of evidence does not indicate that alcohol intake is an independent risk factor for gastric cancer.

In this study, the strongest inverse association was between serum pepsinogen I levels and stomach cancer risk. A low pepsinogen I level is related to the presence of intestinal metaplasia of the stomach,[39] a precursor lesion of gastric cancer.[40] Study participants with a pepsinogen I level of less than 20 ng/ml had a ten-fold greater risk for the intestinal, but not the diffuse histological type of gastric cancer. In spite of this strong association, less than one-third of the intestinal cancer cases had a low pepsinogen I level. Furthermore, the association was primarily in patients who were diagnosed with stage 3 or 4 disease. This suggests that, in our study population, pepsinogen I would not be a useful screening test for stomach cancer.

An inverse association was also observed between serum ferritin and gastric cancer. Ferritin is the major intracellular storage protein for iron in the body.[41] It is found in all tissues, and its concentration in the serum is directly related to available iron stores. Others have also found that a low serum ferritin level increases the risk for stomach cancer.[42] They suggested that the inverse

association between serum ferritin and gastric cancer is related to the observation that achlorhydria diminishes the absorption of dietary iron in the gastric mucosa, and achlorhydria increases the risk for gastric cancer. It is possible that achlorhydria is the common entity that precedes both the reduction of serum ferritin levels and the diagnosis of gastric cancer.

There was an inverse association in the intake of vegetables and fruits with gastric cancer risk. The more commonly eaten vegetables in the study population were cabbage, lettuce and tomatoes which accounted for 60% of all vegetables consumed. Papayas, oranges, apples, guavas and mangoes accounted for 66% of the total amount of consumed fruits. Although this study has the advantage of having obtained the dietary data prospectively before the cases of stomach cancer were identified, one limitation is that the dietary intake was based on only a 24-h diet recall. Dietary studies of gastric cancer have often found an inverse association with the intake of vegetables[28, 31, 33–35, 37, 43] and fruits,[28, 31, 33, 34, 36] but there have been other studies which have not shown a similar association.[26, 29]

β-Carotene is frequently found in various vegetables and fruits, but our serum study showed only a weak inverse association of β-carotene with gastric cancer. There was no association with serum retinol or α-tocopherol. Further analysis revealed that the inverse association of serum β-carotene with gastric cancer was mainly in patients diagnosed within five years of their entry into the study, indicating that the low β-carotene levels could result from the metabolic effects of the pre-clinical gastric tumor. More work is needed in studying the association of vegetables and fruits with gastric cancer.

No relation was found in this investigation between gastric cancer and body mass index, physical activity, serum cholesterol, serum uric acid or hematocrit levels. Other studies have also reported no association between gastric cancer and some of these factors.[44–47]

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