Impact of Fasting Plasma Glucose Levels on Gastric Cancer Incidence in a General Japanese Population

The Hisayama Study

HAJIME YAMAGATA, MD[1]
YUTAKA KIYOHARA, MD[1]
SHOTARO NAKAMURA, MD[1]
MICHIAKI KUBO, MD[1]
YUMIHIRO TANIZAKI, MD[1]
TAKAYUKI MATSUMOTO, MD[1]
KEIICHI TANAKA, MD[1]
ISAO KATO, MD[1]
TOMOKO SHIROTA, MD[2]
MITSUO IIDA, MD[1]

OBJECTIVE — Several studies have shown associations between diabetes and various types of cancer other than gastric cancer. The aim of this cohort study was to evaluate the impact of fasting plasma glucose (FPG) levels on gastric cancer occurrence.

RESEARCH DESIGN AND METHODS — A total of 2,466 Japanese subjects aged ≥40 years were stratified into three groups according to FPG tertiles (<5.3 mmol/l, low FPG; 5.3–5.8 mmol/l, modest FPG; >5.8 mmol/l, high FPG) and followed up prospectively for 9 years.

RESULTS — During the follow-up, 66 subjects experienced gastric cancer. In men, the age-adjusted incidences were significantly higher in the modest-FPG (7.0 per 1,000 person-years, $P < 0.05$) and high-FPG (7.2, $P < 0.05$) groups than in the low-FPG group (2.2). In women, the high-FPG group also had a significantly higher age-adjusted incidence of gastric cancer compared with the low-FPG group (2.5 vs. 0.8, $P < 0.05$). The multivariate analysis with Cox's proportional hazards model revealed that the risks of gastric cancer in the modest-FPG (relative risk [RR] 2.3 [95% CI 1.1–5.0]) and high-FPG (3.1 [1.5–6.4]) groups were significantly higher than that in the low-FPG group, even after adjusting for other comprehensive risk factors, including *Helicobacter pylori* status, smoking, and dietary factors. However, this FPG-cancer association was observed only among *H. pylori*–seropositive subjects.

CONCLUSIONS — Our findings suggest that a modest increase in FPG is a risk factor for gastric cancer and that hyperglycemia is a possible cofactor increasing the risk posed by *Helicobacter pylori* infection.

Diabetes Care 28:789–794, 2005

The Japanese population is characterized by a high morbidity from gastric cancer and a high prevalence of *Helicobacter pylori* infection, especially in middle-aged and elderly individuals (1). We have previously reported a significant relationship between infection with *H. pylori* and a subsequent occurrence of gastric cancer for men in a general Japanese population (2). However, only a small percentage of people with *H. pylori* infection develop gastric cancer, indicating that *H. pylori* cannot be the only etiologic factor of gastric cancer; other cofactors must affect the relationship between *H. pylori* infection and the development of gastric cancer.

On the other hand, a possible association between diabetes and an increase in mortality from malignant neoplasm has been discussed for many years (3). Several prospective cohort studies have examined the associations between diabetes and total cancers (4–7). Among them, three studies have demonstrated that diabetes is associated with an excess risk for all cancers (4–6), while another study could not confirm a positive association between diabetes and total cancer (7). Several recent studies have shown associations between diabetes and cancer in the pancreas (8,9), liver (8,10), and large bowel (11,12). To our knowledge, none of the previous studies evaluated the impact of hyperglycemia on the development of gastric cancer.

In the present investigation, we prospectively examined the relationship between fasting plasma glucose (FPG) levels and gastric cancer occurrence in a general Japanese population, taking *H. pylori* infection as well as other comprehensive risk factors into consideration.

RESEARCH DESIGN AND METHODS

— The Hisayama study is a prospective epidemiological study of ongoing cardiovascular disease and malignancy in Hisayama Town, a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in Japan. The study design and characteristics of the subject population have been described in detail elsewhere (2,13,14). In 1988, 2,742 residents aged ≥40 years (80.1% of the total population in that age population) underwent a screening examination. After excluding 132 individuals with a prior history of gastrectomy or gastric cancer, 141 individuals who had

From the [1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; and the [2]Department of Health Promotion, School of Health and Nutrition Sciences, Nakamura-Gakuen University, Fukuoka, Japan.

Address correspondence and reprint requests to Hajime Yamagata, MD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: yamagen@intmed2.med.kyushu-u.ac.jp.

Received for publication 29 July 2004 and accepted in revised form 10 January 2005.

Abbreviations: FPG, fasting plasma glucose.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

eaten breakfast on the day of the screening examination, and 3 individuals who died during the examination period, a total of 2,466 subjects were enrolled in the present study.

Follow-up survey

The population was followed up for 9 years, from December 1988 through November 1997, by repeated health check-ups every 1–2 years. For subjects who did not undergo regular check-ups or who moved out of the town, the health status was checked every year by mail or telephone. In addition, a daily monitoring system was established by the study team and local physicians or members of the Division of Health and Welfare of the town. To identify any occurrence of gastric cancer in the cohort, we reviewed radiographic, endoscopic, and biopsy records for the stomach at local clinics or general hospitals within and around Hisayama Town. We also checked all the records of the annual mass screenings for gastric cancer by means of barium X-ray examination. Further, to find any concealed gastric cancer, autopsy examinations were performed on 212 (79.1%) of a total of 268 subjects who died during the follow-up period. The diagnosis of gastric cancer was confirmed by histological examination of resected specimens obtained by gastrectomy, endoscopic mucosal resection, or autopsy.

During the follow-up period, only 1 subject was lost, and 71 gastric cancers were identified in 66 subjects (48 men and 18 women); 5 subjects (7.6%) each had two gastric cancers, and 2 concealed cases (3.0%) were diagnosed at autopsy. The time interval from the baseline screening to the diagnosis of gastric cancer ranged from 0.5 to 8.7 years (mean 5.0 years).

Laboratory testing and risk factor measurement

For the measurement of FPG levels, blood was drawn from an antecubital vein using vacutainer tubes with heparin, EDTA, and fluoridated natrium. The blood sampling was undertaken between 8:00 A.M. and 10:30 A.M. after an overnight fast of at least 12 h. Plasma glucose was determined by the glucose-oxidase method. Diabetes was determined by either a 75-g oral glucose tolerance test (1998 World Health Organization criteria), FPG levels (≥7.0 mmol/l), or a medical history of diabetes. The numbers of subjects with diabetes diagnosed by each type of diagnosis were 294, 4, and 9, respectively. Based on the distribution of FPG levels, subjects were classified into tertile groups: low FPG (<5.3 mmol/l), modest FPG (5.3–5.8 mmol/l), and high FPG (>5.8 mmol/l).

Serum IgG antibodies to *H. pylori* were measured by means of a quantitative enzyme immunoassay using a commercial kit (HM-CAP; Enteric Products, Westbury, NY). The assay values were interpreted as positive, negative, or indeterminate, based on the manufacturer's instructions. Serum cholesterol levels were determined by an enzymatic autoanalyzer (TBA-80S; Toshiba, Tokyo, Japan). Height and weight were measured with the subject in light clothes without shoes, and the BMI (kg/m^2) was calculated. Dietary factors were obtained by a semiquantitative food frequency method that was previously validated in a prior study (15). A self-administered questionnaire concerning food intake over the previous year, which included 70 food items, was completed before the start of the study by each participant and was checked by experienced dietitians and nutritionists by showing food models of actual size in the survey. The average daily nutrient intakes, including total energy, total fat, salt, vitamin A, vitamin B_1, vitamin B_2, vitamin C, and dietary fibers, were calculated using the 4th revision of the Standard Tables of Food Composition in Japan (16), and the nutritional elements were adjusted for energy intake using the method of Willet and Stampfer (17). Information about smoking habits, alcohol intake, and history of peptic ulcer disease were obtained by means of a questionnaire administered to each subject, and the former two items were categorized as in current use or not in current use.

Statistical analysis

The SAS computer package (18) was used for all statistical analyses. Mean values of the possible risk factors were adjusted for age by the covariance method and were compared among tertile groups of FPG using Fisher's least significant difference method. The frequencies of risk factors were compared by the Mantel-Haenszel χ^2 test after adjusting for age by the direct method. The incidence of gastric cancer was calculated by the person-year method, and its differences among groups with different FPG levels were analyzed by means of Cox's proportional hazards model (19). The risk factor–adjusted relative risks (RRs) were also estimated using Cox's proportional hazards model and are expressed together with 95% CIs. In the multivariate analysis, we used a stepwise method, setting the significance level for entry and keeping it at 0.1. Only 19 subjects who did not develop gastric cancer dropped out due to missing values in the covariates, while no case with gastric cancer dropped out of the analysis. For age adjustment, all study subjects were used as a standard population.

This study was conducted with the approval of the ethics committee of Kyushu University, and written informed consent for medical research was obtained from the study participants.

RESULTS — Table 1 compares the age-adjusted mean values or frequencies of possible risk factors for gastric cancer among the three FPG groups by sex. In men and women, the mean age increased significantly with an increase in FPG levels, and diabetes was found most frequently in the high-FPG group. Similarly, mean values of BMI and total cholesterol and frequency of alcohol intake in both sexes increased significantly with increases in FPG levels. The frequency of smoking habits in men decreased significantly with elevated FPG levels. The frequency of *H. pylori* infection and history of peptic ulcer disease and mean values of dietary factors were not found to be related to FPG levels in either sex.

As shown in Table 2, the age-adjusted incidence of gastric cancer of 5.6 per 1,000 person-years for men was significantly higher than that of 1.3 per 1,000 person-years for women. In men, the age-adjusted incidence was significantly higher in the modest-FPG (7.0, $P < 0.05$) and high-FPG (7.2, $P < 0.05$) groups than in the low-FPG (2.2) group. In women, the high-FPG group also had a significantly higher age-adjusted incidence of gastric cancer (2.5, $P < 0.05$) compared with that of the low-FPG group (0.8). The age- and sex-adjusted risks of gastric cancer in the modest-FPG (RR 2.3 [95% CI 1.1–5.1]) and high-FPG (3.0 [1.5–6.4]) groups were significantly higher than those in the low-FPG group (Fig. 1). These associations remained unchanged even after adjustment for age, sex, BMI, serum cholesterol, *H. pylori* se-

Table 1—*Age-adjusted mean values or frequencies of risk factors for gastric cancer according to fasting plasma glucose levels by sex*

	Men			Women		
Risk factors	Low FPG	Modest FPG	High FPG	Low FPG	Modest FPG	High FPG
n	278	326	424	551	484	403
Cases	5	19	24	3	4	11
Age (years)	56.5	56.2	59.1*†	57.0	58.5*	61.5*†
FPG (mmol/l)	5.01	5.55*	6.75*†	4.99	5.54*	6.74*†
Diabetes (%)	2.2	2.9	33.8*†	0.8	1.7	31.0*†
BMI (kg/m^2)	22.1	23.1*	23.6*†	22.4	23.2*	23.6*†
Total cholesterol (mmol/l)	4.97	5.08	5.27*†	5.52	5.46	5.71*†
Alcohol intake (%)	24.0	30.5	39.1*†	0.5	1.6	2.8*
Smoking habits (%)	55.4	48.5*	45.4*	6.1	7.2	7.2
H. pylori infection (%)	71.8	72.8	71.4	65.7	62.0	61.3
History of peptic ulcer disease (%)	27.0	21.3	22.1	9.9	9.6	8.0
Total energy intake (kcal/day)	1,826	1,901	1,863	1,541	1,525	1,510
Total fat intake (g/day)	44.3	43.4	43.8	49.4	49.4	49.4
Salt intake (g/day)	12.3	12.3	12.2	12.4	12.6	12.1
Vitamin A intake (IU/day)	2,392	2,465	2,369	2,893	2,922	2,836
Vitamin B_1 intake (mg/day)	0.72	0.70	0.69	0.77	0.77	0.79
Vitamin B_2 intake (mg/day)	1.03	1.01	1.03	1.15	1.16	1.18
Vitamin C intake (mg/day)	61.6	63.4	60.2	76.7	77.5	76.7
Dietary fiber intake (g/day)	9.2	9.1	8.9	11.0	11.1	11.2

*$P < 0.05$ vs. low FPG; †$P < 0.05$ vs. modest FPG.

ropositivity, smoking habits, alcohol intake, history of peptic ulcer disease, and dietary factors, including intake of total energy, total fat, salt, vitamin A, vitamin B_1, vitamin B_2, vitamin C, and dietary fibers. In addition, we performed the same analysis with all subjects except for those who developed gastric cancer in the first 2 years of the follow-up period to decrease the influence of the concealed gastric cancers at baseline. As a result, the age- and sex-adjusted RR of gastric cancer was 2.2 (95% CI 0.9–4.9) in the modest-FPG group and 2.9 (1.3–6.3) in the high-FPG group. The magnitude of the cancer risk in the modest- and high-FPG groups was almost the same as that obtained in the analysis of all subjects, although no statistically significant difference was found in the modest-FPG group, probably due to the small number of cases.

The seroprevalence of *H. pylori* was 66.6% for all subjects, 77.3% for those with gastric cancer, and 66.3% for the subjects who did not develop gastric cancer. We then compared the risk of gastric cancer among FPG groups under stratification by *H. pylori* status (Fig. 2). Among *H. pylori*–positive subjects, the age- and sex-adjusted risks of gastric cancer were significantly higher in the modest-FPG (RR 3.5 [95% CI 1.3–9.5]) and high-FPG (4.2 [1.6–11.1]) groups than in the low-FPG group, whereas no such differences were found in *H. pylori*–negative subjects.

CONCLUSIONS — Our findings indicate a positive association between elevated FPG levels and gastric cancer incidence in men and women, an association that remains significant even after adjusting for other risk factors such as age, sex, BMI, serum cholesterol, *H. pylori* seropositivity, smoking habits, alcohol intake, history of peptic ulcer disease, and dietary factors. The risk of gastric cancer was found to be increased not only in the high-FPG group, of which approximately one-third was diagnosed as diabetic, but also in the modest-FPG group, in which only a small number of subjects fulfilled the diagnostic criteria of diabetes. These results suggest that subjects with high FPG levels may have an increased risk of developing gastric cancer, even if they have not developed diabetes. In addition, a stratified analysis showed increased FPG levels to be an independent risk factor for gastric cancer only among *H. pylori*–seropositive subjects; no such risk was observed among *H. pylori*–seronegative subjects.

In this study, the age-adjusted inci-

Table 2—*Age-adjusted incidence of gastric cancer according to FPG levels*

	Men (n = 1,028)		Women (n = 1,438)		All (n = 2,466)	
	n	Incidence (95% CI)	*n*	Incidence (95% CI)	*n*	Incidence (95% CI)
Low FPG (<5.3 mmol/l)	5	2.2 (0.3–4.1)	4	0.8 (0.0–1.6)	9	1.4 (0.5–2.2)
Modest FPG (5.3–5.8 mmol/l)	19	7.0 (3.9–10.2)*	3	0.6 (−0.1 to 1.3)	22	3.3 (2.0–4.7)*
High FPG (>5.8 mmol/l)	24	7.2 (4.1–10.3)*	11	2.5 (1.0–4.1)*	35	4.5 (2.8–6.2)*
All	48	5.6 (4.0–7.3)	18	1.3 (0.7–1.9)†	66	3.1 (2.4–3.9)

Incidence rates are expressed per 1,000 person-years. *$P < 0.05$ vs. low FPG; †$P < 0.05$ vs. men.

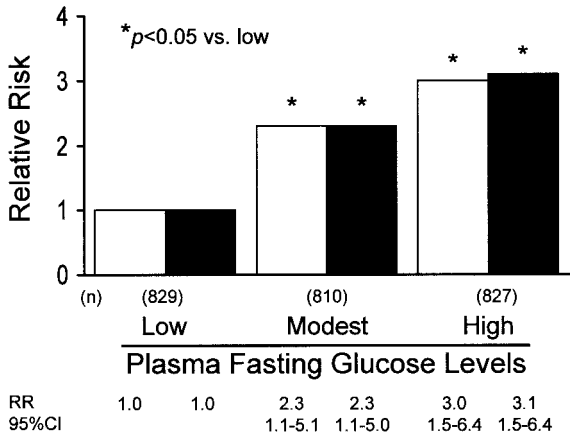

Figure 1—*Age- and sex-adjusted (□) and multivariate-adjusted (■) RR of gastric cancer of the modest-FPG (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group. In the multivariate analysis, the RR is adjusted for age, sex, BMI, serum cholesterol,* H. pylori *seropositivity, smoking habits, alcohol intake, history of peptic ulcer disease, and dietary factors (intake of total energy, total fat, salt, vitamin A, vitamin B_1, vitamin B_2, vitamin C, and dietary fibers) using stepwise Cox's proportional hazards model.*

dence of gastric cancer was 5.6 per 1,000 person-years for men and 1.3 for women, which is higher than that found in previous studies in Japan (0.7–2.0 per 1,000 person-years for men and 0.3–0.7 for women) (20–23). This discrepancy seems to be due to differences in the study design as well as in the age structures or regions examined. The previous studies were registration studies, while ours was a prospective cohort study in which we carried out an intensive and accurate survey of gastric cancer, including autopsy examination of 79% of the deceased subjects to find any concealed gastric cancer. It is therefore supposed that our study results reflect the actual cancer incidence in the Japanese population.

The mechanisms for increased risk of gastric cancer in hyperglycemia remain obscure. One possible explanation is that hyperglycemia and its related conditions act directly as a carcinogenic factor. Dandona et al. (24) have demonstrated in a clinical study with diabetic subjects and healthy volunteers that diabetes is associated with increased production of reactive oxygen species and greater oxidative damage to DNA. In an experimental study, high glucose itself was shown to induce DNA damage (25). Thus, it is possible that increased production of reactive oxygen species or high glucose itself contributes to DNA damage, which may lead to mutational changes in oncogenes and tumor suppressor genes, and thereby to the development of gastric cancer.

Another possible explanation is that hyperinsulinemia is related to gastric carcinogenesis. Patients with hyperglycemia are prone to insulin resistance, which leads to higher levels of blood insulin. McKeown-Eyssen (26) and Giovannucci (27,28) showed in epidemiological and experimental studies that hyperinsulinemia is involved in colonic carcinogenesis. These investigators independently hypothesized that well-specified risk factors for colorectal cancer, such as obesity, physical inactivity, alcohol consumption, or a typical western diet, contribute to insulin resistance. Ogihara et al. (29) have demonstrated that insulin enhances the stimulatory effects of epidermal growth factor on the proliferation of cultured gastric epithelial cells obtained from the guinea pig. It can be speculated that an increase in cell proliferation predisposes the gastric mucosa to genetic or epigenetic alterations and, therefore, to carcinogenesis (30,31).

Finally, it is postulated that gastric cancer and hyperglycemia share common genetic or environmental risk factors. However, no common genetic background or common provisional risk factor other than age has been identified to date. Furthermore, that hypothesis cannot be supported by our results; we failed to show any significant correlation of FPG levels with *H. pylori* status or with dietary factors. Further, although smoking habits have been presumed to be a risk factor for gastric cancer (32), the frequency of smoking habits in men was rather low in the high- and modest-FPG groups relative to that in the low-FPG group.

Based on numerous epidemiologic and experimental studies, *H. pylori* has been regarded to be a definite risk factor for gastric cancer (2,33). Although the precise pathogenetic role of *H. pylori* in gastric carcinogenesis remains unclear, it has been clarified that this organism contributes to modifications in epithelial cell proliferation (34,35), which may be the initiating event in a cascade culminating in the development of gastric cancer. However, an increased risk of gastric cancer by *H. pylori* infection notwithstanding, the majority of *H. pylori*–infected subjects do not develop gastric cancer. As such, *H. pylori* is not the absolute oncogenic factor for gastric cancer, and there must be other critical cofactors contributing to the risk posed by *H. pylori* infection. Our stratified analysis showed increased FPG levels to be a significant risk factor for gastric cancer only among *H. pylori*–seropositive subjects; this link was not observed among *H. pylori*–seronegative subjects. This result indicates that hyperglycemia is a possible cofactor increasing the risk posed by *H. pylori* infection. In a clinical study, Acbay et al. (36) demonstrated that *H. pylori* gastritis enhances glucose- and meal-stimulated insulin release, probably by increasing gastrin secretion. Thus, the enhanced effect of hyperglycemia on the *H. pylori*–cancer as-

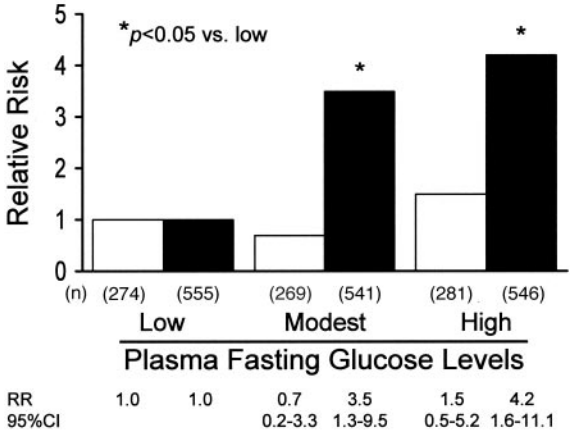

Figure 2—*Age- and sex-adjusted RR of gastric cancer of the modest (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group under stratification by* H. pylori *status.* □, H. pylori *seronegative;* ■, H. pylori *seropositive.*

sociation may be explained partially by hyperinsulinemia. Another possible explanation for this phenomenon may be that hyperglycemia affects *H. pylori* and its infection status or stimulates its carcinogenic effects. However, the association between *H. pylori* infection and diabetes is controversial in the literature. A higher prevalence of *H. pylori* infection in diabetic than in control subjects has been reported in some studies (37,38), whereas other studies have found no association between *H. pylori* and diabetes (39,40). In this study, we found no significant correlation between FPG levels and *H. pylori* status. It may be speculated that increased reactive oxygen–related damage to DNA and genetic or epigenetic alterations in gastric mucosa induced by hyperglycemia or associated hyperinsulinemia encourage a modifying effect of *H. pylori* on epithelial cell proliferation, which may be the initial step in a cascade of gastric carcinogenesis. Given the range of findings, this hypothesis requires further consideration.

Several limitations of our study should be discussed. The primary limitation of our study, which is typical of most prospective studies, is that changes in other potentially confounding factors for the development of gastric cancer were not reassessed over time in our subjects. It is therefore possible that as a result of treatment for diabetes, greater modification of other risk factors occurred in diabetic than in nondiabetic subjects. In our subjects, however, the risk of gastric cancer was increased even in association with pre-diabetic hyperglycemia, which is not subject to medical treatment. In addition, the carcinogenic effects of risk factors usually continue for a long period (41–43). Thus, bias of this kind was considered to be small in the present study.

A second limitation is that an average follow-up time of 5 years does not account for the much longer latency or induction period of gastric cancer. Accordingly, we cannot eliminate the possibility that there were concealed gastric cancers that had already developed by the time of the baseline examination, though this limitation is a common problem for a large majority of other registration studies of gastric cancer. However, the prevalence of gastric cancer in healthy subjects has been found to be low (0.12%) in a nationwide mass screening in Japan (44). In addition, our analysis of all subjects except for those who developed gastric cancer in the first 2 years of the follow-up period produced results similar to those obtained from our analysis of all subjects. We therefore believe that concealed cancers were rare at the baseline examination and that the influence of this bias is small.

The final limitation is that only a small number of gastric cancer cases developed in our cohort, indicating a high possibility of bias in the results. Nonetheless, we believe that the findings of our study represent an accurate incidence of gastric cancer and its association with hyperglycemia, since we performed the study using a highly accurate method for determining all gastric cancer cases.

In conclusion, we found the elevation of FGP levels to be a significant risk factor for gastric cancer in men and women. The contribution of FPG to the subsequent occurrence of gastric cancer was significant in *H. pylori*–seropositive subjects and not in *H. pylori*–seronegative subjects. These findings suggest that some interaction between hyperglycemia and *H. pylori* infection contributes to the development of gastric cancer or that hyperglycemia is a possible cofactor increasing the risk posed by *H. pylori* infection. Further study is necessary to clarify the pathogenetic role of hyperglycemia as well as of *H. pylori* infection and their interaction in gastric carcinogenesis.

Acknowledgments— This study was supported in part by a grant-in-aid for scientific research (C:13670370) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References

1. The EUROGAST Study Group: An international association between *Helicobacter pylori* infection and gastric cancer. *Lancet* 341:1359–1362, 1993
2. Yamagata H, Kiyohara Y, Aoyagi K, Kato I, Iwamoto H, Nakayama K, Shimizu H, Tanizaki Y, Arima H, Shinohara N, Kondo H, Matsumoto T, Fujishima M: Impact of *Helicobacter pylori* infection on gastric cancer incidence in a general Japanese population: the Hisayama study. *Arch Int Med* 160:1962–1968, 2000
3. Kessler II: Cancer and diabetes mellitus: a review of the literature. *J Chron Dis* 23: 579–600, 1971
4. Steenland K, Nowlin S, Palu S: Cancer incidence in the National Health and Nutrition Survey I. Follow-up data: diabetes, cholesterol, pulse and physical activity. *Cancer Epidemiol Biomarkers Prev* 4:807–811, 1995
5. Levine W, Dyer AR, Shekelle RB, Schoenberger JA, Stamler J: Post-load plasma glucose and cancer mortality in middle-aged men and women: 12-year follow-up findings of Chicago Heart Association Detection Project in Industry. *Am J Epidemiol* 131:254–262, 1990
6. Eschwege E, Charles MA, Simon D, Thibult N, Balkau B: From policemen to policies: what is the future for 2-h glucose? The Kelly West Lecture, 2000. *Diabetes Care* 24:1945–1950, 2001
7. Smith GD, Egger M, Shipley MJ, Marmot MG: Post-challenge glucose concentration, impaired glucose tolerance, diabetes, and cancer mortality in men. *Am J Epidemiol* 136:1110–1114, 1992
8. Wideroff L, Gridley G, Mellemkjaer L, Chow WH, Linet M, Keehn S, Borch-Johnsen K, Olsen JH: Cancer incidence in a population-based cohort of patients hospitalized with diabetes mellitus in Denmark. *J Natl Cancer Inst* 89:1360–1365, 1997
9. Everhart J, Wright D: Diabetes mellitus as a risk factor for pancreatic cancer: a meta-analysis. *JAMA* 273:1605–1609, 1995
10. Adami HO, Chow WH, Nyren O, Berne C, Linet MS, Ekbom A, Wolk A, McLaughlin JK, Fraumeni JF Jr: Excess risk of primary liver cancer in patient with diabetes mellitus. *J Natl Cancer Inst* 88: 1472–1477, 1996
11. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, Michels KB, Speizer FE, Giovannucci E: Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. *J Natl Cancer Inst* 91:542–547, 1999
12. Nilsen TL, Vatten LJ: Prospective study of colorectal cancer risk and physical activity, diabetes, blood glucose and BMI: exploring the hyperinsulinaemia hypothesis. *Br J Cancer* 84:417–422, 2001
13. Katsuki S: Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* 21B:64–89, 1966
14. Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Nomiyama K, Ohmori S, Yoshitake T, Shinkawu A, Hasuo Y, Fujishima M: Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama study. *Diabetologia* 36:1198–1203, 1993
15. Shirota T, Yoshizumi E. Accuracy of nutritional survey using the simple method. *Jpn J Public Health* (in Japanese) 37:100–108, 1990
16. Resources Council of the Science and

Technology Agency: *Standard Tables of Food Composition in Japan*. 4th ed. Tokyo, Ministry of Finance Printing Bureau, 1982 (in Japanese)
17. Willet W, Stampfer MJ: Total energy intake: implications for epidemiologic analysis. *Am J Epidemiol* 124:17–27, 1986
18. *SAS/STAT User's Guide*. Version 6. Cary, NC, SAS Institute, 1989
19. Cox DR: Regression models and life-tables. *J R Stat Soc (Series B)* 34:187–220, 1972
20. The Research Group for Population-based Cancer Registration in Japan: Cancer incidence in Japan, 1985–89: re-estimation based on data from eight population-based cancer registries. *Jpn J Clin Oncol* 28:54–67, 1998
21. Kaneko S, Yoshimura T: Time trend analysis of gastric cancer incidence in Japan by histological types, 1975–1989. *Br J Cancer* 84:400–405, 2001
22. Lambert R, Guilloux A, Oshima A, Pompe-Kirn V, Bray F, Parkin M, Ajiki W, Tsukuma H: Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. *Int J Cancer* 97:811–818, 2002
23. Nishino Y, Suzuki Y, Ohmori K, Hozawa A, Ogawa K, Kuriyama S, Tsubono Y, Shibuya D, Tsuji I, Fukao A, Hisamichi S: Cancer incidence profiles in the Miyagi Cohort Study. *J Epidemiol* 14 (Suppl. 1): S7–S11, 2004
24. Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, Nicotera T: Oxidative damage to DNA in diabetes mellitus. *Lancet* 347:444–445, 1996
25. Lorenzi M, Montisano DF, Toledo S, Barrieux A: High glucose induces DNA damage in cultured human endothelial cells. *J Clin Invest* 77:322–325, 1986
26. McKeown-Eyssen G: Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? *Cancer Epidemiol Biomarkers Prev* 3:687–695, 1994
27. Giovannucci E: Insulin and colon cancer. *Cancer Causes Control* 6:164–179, 1995
28. Giovannucci E: Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J Nutr* 131 (11 Suppl.): 3109S–3120S, 2001
29. Ogihara S, Yamada M, Saito T, Shono M, Rokutan K: Insulin potentiated mitogenic effect of epidermal growth factor on cultured guinea pig gastric mucous cells. *Am J Physiol* 271:G104–G112, 1996
30. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE: Increased cell division as a cause of human cancer. *Cancer Res* 50:7415–7421, 1990
31. Farber E: Cell proliferation as a major risk factor for cancer: a concept of doubtful validity. *Cancer Res* 55:3759–3762, 1995
32. Inoue M, Tajima K, Yamamura Y, Hamajima N, Hirose K, Nakamura S, Kodera Y, Kito T, Tominaga S: Influence of habitual smoking on gastric cancer by histologic subtype. *Int J Cancer* 81:39–43, 1999
33. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ: *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med* 345:784–789, 2001
34. Anti M, Armuzzi A, Gasbarrini A, Gasbarrini G: Importance of changes in epithelial cell turnover during *Helicobacter pylori* infection in gastric carcinogenesis. *Gut* 43 (Suppl. 1):S27–S32, 1998
35. Higashi H, Tsutsumi R, Muto S, Sugiyama T, Azuma T, Asaka M, Hatakeyama M: SHP-2 tyrosine phosphatase as an intracellular target of *Helicobacter pylori* CagA protein. *Science* 295:683–686, 2002
36. Acbay O, Celik AF, Gundogdu S: Does *Helicobacter pylori*-induced gastritis enhance food-stimulated insulin release? *Dig Dis Sci* 41:1327–1331, 1996
37. Oldenburg B, Diepersloot RJ, Hoekstra JB: High seroprevalence of *Helicobacter pylori* in diabetes mellitus patients. *Dig Dis Sci* 41:458–461, 1996
38. Gentile S, Turco S, Oliviero B, Torella R: The role of autonomic neuropathy as a risk factor of *Helicobacter pylori* infection in dyspeptic patients with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 42: 41–48, 1998
39. Gasbarrini A, Ojetti V, Pitocco D, De Luca A, Franceschi F, Candelli M, Sanz Torre E, Pola P, Ghirlanda G, Gasbarrini G: *Helicobacter pylori* infection in patients affected by insulin-dependent diabetes mellitus. *Eur J Gastroenterol Hepatol* 10:469–472, 1998
40. Xia HH, Talley NJ, Kam EP, Young LJ, Hammer J, Horowitz M: *Helicobacter pylori* infection is not associated with diabetes mellitus, nor with upper gastrointestinal symptoms in diabetes mellitus. *Am J Gastroenterol* 96:1039–1046, 2001
41. Inoue M, Tajima K, Hirose K, Kuroishi T, Gao CM, Kitoh T: Life-style and subsite of gastric cancer: joint effect of smoking and drinking habits. *Int J Cancer* 56:494–499, 1994
42. Hansson LE, Nyren O, Bergstrom R, Wolk A, Lindgren A, Baron J, Adami HO: Diet and risk of gastric cancer: a population-based case-control study in Sweden. *Int J Cancer* 55:181–189, 1993
43. Hansson LE, Baron J, Nyren O, Bergstrom R, Wolk A, Lindgren A, Adami HO: Early-life risk indicators of gastric cancer: a population-based case-control study in Sweden. *Int J Cancer* 57:32–37, 1994
44. Hisamichi S: Screening for gastric cancer. *World J Surg* 13:31–37, 1989