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

The Hisayama Study

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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.

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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

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Abbreviations: FPG, fasting plasma glucose.

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

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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.

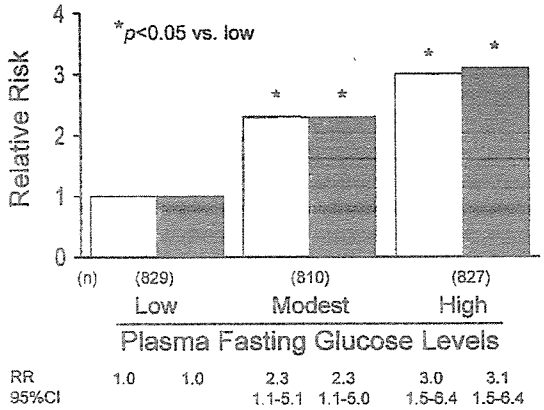

Figure 1—*Age- and sex-adjusted (□) and multivariate-adjusted (■) RR of gastric cancer of the modest-FPG (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group. In the multivariate analysis, the RR is adjusted for age, sex, BMI, serum cholesterol, H. 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-

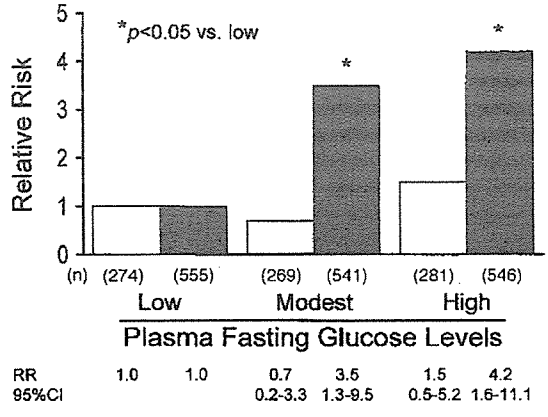

Figure 2—*Age- and sex-adjusted RR of gastric cancer of the modest (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group under stratification by* H. pylori *status.* □, H. pylori *seronegative;* ■, H. pylori *seropositive.*

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.

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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

Relationship Between C-Reactive Protein and Glucose Levels in Community-Dwelling Subjects Without Diabetes

The Hisayama Study

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C-reactive protein (CRP), a marker of systemic inflammation, is emerging as an independent risk factor for cardiovascular disease (1,2). It has also been reported that serum CRP levels are elevated in patients with impaired glucose tolerance (IGT) (3) or diabetes (4). A few prospective studies have shown that increased CRP levels are an independent risk factor for future diabetes (5,6). Although these findings indicate that CRP levels in peripheral blood are closely associated with glucose levels, it remains unclear whether a relationship exists between CRP levels and plasma glucose levels in the pre-diabetic range. The purpose of the present study was to investigate the relationship between CRP concentrations and pre-diabetic plasma glucose levels in a general Japanese population.

RESEARCH DESIGN AND METHODS — A population-based prospective study of cardiovascular disease has been underway since 1961 in the town of Hisayama, Kyushu Island, Japan. In 1988, as a part of the study, a cross-sectional diabetes survey of Hisayama residents was conducted (7). Of all 3,227 residents aged 40–79 years in the town registry, 2,587 (80.2%) consented to take part in a comprehensive assessment, including a fasting 75-g oral glucose tolerance test. After excluding 82 nonfasting participants, 15 of whom failed to complete the oral glucose tolerance test, 302 with diabetes based on the American Diabetes Association (ADA) criteria (8), and 61 without serum samples for the CRP measurement, the final study group included 2,127 subjects (882 men and 1,245 women).

Overnight fasting and 2-h postload plasma glucose levels were determined by the glucose-oxidase method, and serum insulin was determined by radioimmunoassay. Total cholesterol, HDL cholesterol, and triglycerides were all determined enzymatically. Serum specimens collected at the time of the CRP measurement were stored at −20°C until 2002. High-sensitivity CRP was analyzed using a modification of the Behring Latex-Enhanced CRP assay on the Behring Nephelometer Analyzer System with a 2% interassay coefficient of variation. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or a diastolic blood pressure ≥90 mmHg and/or current treatment with antihypertensive agents. A questionnaire investigated smoking habits and alcohol intake, and both were classified as either currently or not currently habitual.

Because the distributions of CRP, fasting insulin, and triglycerides are skewed, these variables were natural log transformed for statistical analysis. The multivariate-adjusted CRP values were calculated by the covariance method and were compared by the Fisher's least significant difference method.

This study was conducted with the approval of the Ethics Committee of Kyushu University, and written informed consent was obtained from each participant.

RESULTS — The mean age was 57 years for both men and women. When the subjects were divided into three groups according to fasting plasma glucose levels, low (<5.6 mmol/l), modest (5.6–6.0 mmol/l), and high (6.1–6.9 mmol/l), the age- and sex-adjusted mean CRP levels significantly increased as the fasting glucose levels rose (0.41 mg/l in low, 0.49 mg/l in modest, and 0.62 mg/l in high fasting glucose level), and the differences between low and modest or high glucose levels were significant ($P < 0.01$). A similar pattern was observed for three 2-h postload glucose levels: low (<5.6 mmol/l), modest (5.6–7.7 mmol/l), and high (7.8–11.0 mmol/l). The age- and sex-adjusted CRP levels were 0.35 mg/l for low, 0.48 mg/l for modest, and 0.59 mg/l for the high postload glucose levels; the values were significantly higher for modest or high levels than for low levels ($P < 0.001$).

To clarify the existence of an independent relationship between each glucose level and CRP, we classified subjects into nine categories according to glucose levels measured at fasting and at 2-h postload and estimated mean CRP level in each category after adjustments for age, sex, fasting insulin, BMI, total cholesterol,

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Abbreviations: ADA, American Diabetes Association; CRP, C-reactive protein; IGT, impaired glucose tolerance.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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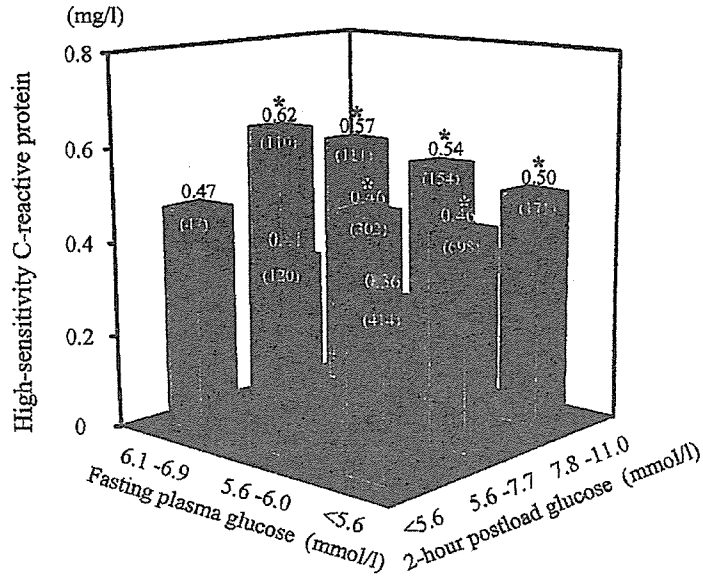

Figure 1—*High-sensitivity C-reactive protein (CRP) levels according to fasting plasma glucose and 2-h postload glucose levels. Multivariate adjustments were made for age, sex, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, hypertension, smoking habits, and alcohol intake. Parentheses indicate the number of subjects. *P < 0.05 vs. category with fasting plasma glucose <5.6 mmol/l and 2-h postload glucose <5.6 mmol/l.*

HDL cholesterol, triglycerides, hypertension, smoking habits, and alcohol intake (Fig. 1). When compared with the category of fasting and postload glucose levels of <5.6 mmol/l, the adjusted CRP levels were significantly higher in the categories of IGT (high postload glucose levels, 7.8–11.0 mmol/l) and the modest postload glucose range (5.6–7.7 mmol/l), irrespective of fasting glucose levels.

CONCLUSIONS— The ADA recently proposed new criteria for diabetes and a lesser degree of impaired glucose regulation, although the criteria to diagnose diabetes and IGT remained as previously defined (8). However, the lower cut-off point defining impaired fasting glucose was reduced from ≥6.1 to ≥5.6 mmol/l. In our study, CRP progressively increased as fasting or postload glucose levels increased. These relationships did not show threshold effects, and CRP levels apparently rose even with the fasting glucose levels corresponding to the newly extended range of the impaired fasting glucose category (5.6–6.0 mmol/l) or with the postload glucose levels under the IGT category (5.6–7.7 mmol/l). These findings support the concept of the new ADA criteria for impaired fasting glucose, in which the expanded range of impaired fasting glucose predicts future diabetes and cardiovascular disease (8). However, when analyzing fasting plasma glucose and 2-h postload glucose levels together, it is apparent that the elevated CRP levels in the new range, as well as in the range of impaired fasting glucose previously defined (6.1–6.9 mmol/l), are mainly due to elevated CRP concentrations according to 2-h postload glucose levels. These findings suggest that the glucose-CRP relationship is stronger for 2-h postload glucose levels than for fasting glucose levels. This hypothesis is in accordance with the findings of previous studies (9,10) showing the predominance of the effects of 2-h postload glucose levels on cardiovascular events.

A limitation is that CRP was measured by a long-term conserved serum at −20°C. It was however confirmed in the Reykjavik Study (11) that CRP concentrations were stable in preserved serum at this temperature for an average of 12 years.

To our knowledge, this is the first report to indicate a direct, positive relationship between CRP and pre-diabetic glucose levels across the normal range. Due to the cross-sectional design of the present study, however, we cannot infer from these results whether this relationship is one of cause or effect. Prospective studies are needed to resolve this question.

References

1. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH: Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 336:973–979, 1997
2. Ridker PM, Buring JE, Shih J, Matias M, Hennekens CH: Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 98:731–733, 1998
3. Temelkova-Kurktschiev T, Henkel E, Koehler C, Karrei K, Hanefeld M: Subclinical inflammation in newly detected type II diabetes and impaired glucose tolerance. *Diabetologia* 45:151, 2002
4. Ford ES: Body mass index, diabetes, and C-reactive protein among U.S. adults. *Diabetes Care* 22:1971–1977, 1999
5. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM: C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 286:327–334, 2001
6. Barzilay JI, Abraham L, Heckbert SR, Cushman M, Kuller LH, Resnick HE, Tracy RP: The relation of markers of inflammation to the development of glucose disorders in the elderly: the Cardiovascular Health Study. *Diabetes* 50:2384–2389, 2001
7. Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Nomiyama K, Ohmori S, Yoshitake T, Shinkawa 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
8. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P: Follow-up report on the diagnosis of diabetes mellitus (Review). *Diabetes Care* 26:3160–3167, 2003
9. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 354: 617–621, 1999
10. Tominaga M, Eguchi H, Manaka H, Iga-

rashi K, Kato T, Sekikawa A: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. *Diabetes Care* 22:920–924, 1999

11. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, Lowe GD, Pepys MB, Gudnason V: C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med* 350: 1387–1397, 2004

The 5-Year Incidence and Risk Factors for Age-Related Maculopathy in a General Japanese Population: The Hisayama Study

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Purpose. To estimate the 5-year incidence and risk factors for age-related maculopathy (ARM) in a representative older Japanese population.

Methods. A population-based cohort study was conducted in 1998 on 1482 Hisayama residents aged 50 years or older, and 961 of these subjects attended the 5-year follow-up examinations in 2003. At both time points, the characteristics of ARM were determined by grading color fundus photographs according to the Wisconsin Age-Related Maculopathy Grading System. Using these cohort data, logistic regression analyses were performed to determine the risk factors for ARM. Nine possible risk factors were examined: age, sex, hypertension, diabetes, hyperlipidemia, smoking, alcohol intake, body mass index, and white blood cell count.

Results. The 5-year incidence of early ARM was 8.5%, and that of late ARM was 0.8%. Men were found to have a significantly higher incidence of late ARM than did women. The incidence of both early and late ARM increased significantly with age. Multiple logistic regression analysis showed that age and smoking were significantly associated with early and late ARM.

Conclusions. The results suggest that the overall 5-year incidence of early ARM is 8.0% and that of late ARM is 0.8% in the general Japanese population and that higher age and smoking are relevant risk factors for early and late ARM in the Japanese. (*Invest Ophthalmol Vis Sci.* 2005;46:1907–1910) DOI:10.1167/iovs.04-0923

Age-related maculopathy (ARM) is a major cause of blindness and severe vision loss in older people in developed countries.[1–3] As the population ages in these countries, ARM will become an increasing public health problem. It is thus crucial that we identify the incidence and risk factors of the disease. Previous population-based studies have investigated several risk factors for ARM, including iris color,[4] hypertension,[5] atherosclerosis,[6] a current smoking habit,[7] and alcohol intake.[8] In addition, we have reported the prevalence and risk factors for ARM in the representative Japanese community of Hisayama, by using cross-sectional data from the Hisayama study.[9] However, although incidence data from the general population would be useful both for counseling patients and understanding the natural course of disease, there has been no population-based study estimating the incidence of ARM in Japan.

The purpose of this study was to describe the 5-year incidence of early and late ARM in a representative Japanese population-based cohort. A further goal was to investigate the major factors that contribute to early and late ARM, by using the cohort data obtained.

Methods

Study Population

The Hisayama Study is an ongoing, prospective population survey that has been conducted in the town of Hisayama since 1961. Hisayama is a suburb of Fukuoka City, which is on the island of Kyushu in the southern part of Japan. The population of the town is approximately 7500, a number that has remained stable for 40 years. According to the 1985 national census, the age distribution of the Hisayama population was almost identical with that of Japan as a whole.[10] The occupations of the subjects were categorized into three types according to the Census for Labor and Products in Japan. Of the population aged 40 to 79 years in the town, 14.6% were engaged in a primary industry (agriculture, fishery, forestry), 29.8% in a secondary industry (mining, construction, manufacture), and 55.6% in a tertiary industry (commerce, restaurant, transport, communication, finance, insurance, supplier of electricity, gas or water, real estate business, service industry, and unclassified official business). The frequency distribution was very similar to that of all Japanese employees in the same age range: 14.5%, 33.4%, and 52.2%, respectively. As part of the follow-up survey, we performed a health examination, including an eye examination, of all Hisayama residents aged 50 years and older. The enrollment criteria, characteristics of the study population and overall design of this study have been described in detail in previous studies.[9] The baseline eye examinations for the Hisayama Study were performed in 1998. Of the 3054 residents in that age group, 1844 (60.4%) consented to participate in the baseline eye examinations. Of these, 349 subjects underwent the health examination at home, whereas 13 subjects refused to participate in the ophthalmic examination. Ultimately, 1482 (48.5%) individuals (596 men and 886 women, 44.3% of the male population and 51.9% of the female population in that age group) underwent baseline eye examinations. Five-year follow-up eye examinations for the Hisayama Study were conducted in 2003. Of the original cohort, 961 (31.4%) persons took part in the examinations, of whom 3 had to be excluded due to ungradable photographs of either eye.

Ophthalmic Examination and Definition of Age-Related Maculopathy

The methods used for the baseline eye examinations have been described in detail elsewhere.[9] Briefly, each participant underwent ophthalmic examinations after pupil dilation with 1.0% tropicamide and 10% phenylephrine. Fundus photographs (45°) were taken (model TRC NW-5 fundus camera; Topcon Corp., Tokyo, Japan), and 35-mm color transparencies were made using slide film (Sensia II Fujichrome; Fujifilm, Tokyo, Japan). In the 5-year follow-up eye examinations, fundus photographs (45°) were taken using a digital fundus camera

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(TRC NW-6SF; Topcon Corp.). In both examinations, we used a similar masked photographic grading technique based on the International ARM Epidemiologic Study Group grading protocol and the grids of the Wisconsin Age-Related Maculopathy Grading System.[11–13] The Wisconsin Age-Related Maculopathy Grading System grid was adapted to the magnification of the camera. This protocol divides ARM into early and late stages. Early-stage ARM was defined by the presence of drusen (soft distinct and soft indistinct) or retinal pigment epithelial (RPE) abnormalities (hyperpigmentation or hypopigmentation),[13] within the grid in the absence of late ARM in either eye. Late-stage ARM was defined as the presence of neovascular age-related macular degeneration (AMD) or geographic atrophy (GA) involving the fovea. Neovascular AMD included serous or hemorrhagic detachment of the RPE or sensory retina, and the presence of subretinal or sub-RPE hemorrhages or subretinal fibrous scar tissue.[13] GA was characterized by sharply edged, roughly round or oval areas of RPE hypopigmentation, with clearly visible choroidal vessels.[13] The minimum area of GA was a circle 175 μm in diameter or larger. These definitions of early and late ARM were used in both the studies in Beaver Dam, Wisconsin, and Blue Mountains eye studies. In our study, two experienced graders (MM, TI), masked to the subject information, assessed the ARM. Inter- and intraobserver variability were analyzed by the κ statistic.[14] The level of agreement between the graders was moderate (0.80–0.86) to substantial for most features.

Data Collection

Blood pressure was measured three times after the subject had rested for at least 5 minutes in the sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. Blood samples were collected from the antecubital vein after an overnight fast. After taking the fasting blood specimen, a 75-g oral glucose tolerance test was performed with a 75-g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical Inc., Shimizu, Japan). Diabetes was defined as a fasting plasma glucose level ≥7.0 mM, a 2-hour postloading glucose level ≥11.1 mM, or a medical history of diabetes. The total cholesterol and serum triglyceride levels were determined enzymatically with an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan), and hyperlipidemia was defined as a total cholesterol level ≥5.7 mM, serum triglyceride level ≥1.7 mM, or the current use of antihyperlipidemic medication. Information on alcohol consumption was obtained by interview, using a questionnaire that ascertained the usual weekly intake of alcoholic beverages over the previous several months. Subjects were classified as either light (<34 g/d of ethanol) or heavy (≥34 g/d of ethanol) drinkers or as nondrinkers. Information on smoking habits was obtained with a standard questionnaire by trained interviewers at the initial examination, and the subjects were classified as either current or past habitual cigarette users or as nonusers. Body height and weight were measured in light clothing without shoes, and the body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. White blood cell counts (WBC) were determined with a counter (STKS; Beckman-Coulter Inc., Hialeah, FL).

Statistical Methods

The 5-year incidences were calculated. Incident early ARM was defined by the appearance at follow-up of either soft drusen or retinal pigmentary abnormalities in either eye of persons in whom no early or late ARM was present at baseline. Incident late ARM was defined by the development at follow-up of neovascular AMD or GA in either eye of persons in whom no early or late ARM was present at baseline. We examined the relationships between the risk factors at baseline and the incidence of early and late ARM. We considered the following nine possible risk factors for ARM: age, sex, hypertension, diabetes, hyperlipidemia, smoking habit, alcohol intake, BMI, and WBC. Age, BMI, and WBC were treated as continuous variables and the others as categorical variables. Each categorical variable was coded either 1 or 0 depending on the presence or absence of the factor, respectively. Mean values were compared by the Student's t-test and frequencies by Pearson's χ^2 test. We estimated the age-adjusted and multivariate odds ratios (ORs) of each potential risk factor by using a stepwise logistic regression analysis. Only variables with $P < 0.05$ were entered into or allowed to remain in the stepwise multivariate regression analysis. Statistical analyses were performed on computer (SAS software; SAS Institute, Cary, NC).[14] A two-sided $P < 0.05$ was considered statistically significant.

TABLE 1. Comparison of Baseline Characteristics between Participants Examined and Those Not Examined at the 5-Year Follow-up

Status at Baseline	Examined (n = 961)	Not Examined (n = 521)
Age (year)	64 ± 8	68 ± 10**
Sex (% men)	40.0	40.5
Early ARM (%)	17.3	15.6
Late ARM (%)	1.0	0.0
Hypertension (%)	46.7	56.4*
Diabetes (%)	11.9	17.9*
Hyperlipidemia (%)	52.2	53.5
Smoking habit (%)	32.9	38.0
Alcohol intake (%)	39.3	38.6
Body mass index (kg/m^2)	23.2 ± 3.1	22.9 ± 3.4
White blood cells (×10^3/mm^3)	5.7 ± 1.5	5.9 ± 1.5

Data are expressed as the mean ± SD or percent.
* $P < 0.05$. ** $P < 0.01$, examined versus not examined.

Ethical Considerations

This study was approved by the Human Ethics Review Committee of Kyushu University Graduate School of Medical Sciences, and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

RESULTS

Table 1 shows the comparison of baseline characteristics between the participants who were examined and those who were not examined at the 5-year follow-up. Those who did not participate at the 5-year follow-up examination were more likely at baseline to be older (68 years vs. 64 years), to have hypertension (56.4% vs. 46.7%), and to have diabetes (17.9% vs. 11.9%). There were no significant differences between the two groups with respect to the presence of ARM or lifestyle habits.

The 5-year incidences of early and late ARM lesions by sex are shown in Table 2. One hundred sixty-six participants with early or late ARM were excluded at the baseline eye examination; in 67 (8.5%) participants incident early ARM developed during the 5-year follow-up period. The incidence of early ARM was slightly but not significantly higher in men than in women. The incidence of retinal pigmentary abnormalities was significantly higher in men than in women. After 13 participants with late ARM were excluded at the baseline eye examination, development of incident late ARM was recorded in 8 (0.8%) participants during the 5-year follow-up period. All participants who had incident late ARM had early ARM at baseline. Five of the eight participants who had late ARM had soft drusen at baseline, and three of the eight had pigmentary abnormalities at baseline. The incidence of late ARM was significantly higher in men than in women. After adjustment for age, men were found to have a significantly higher incidence of late ARM than were women (OR, 2.62; 95% confidence interval [CI], 1.18–5.82). The incidences of GA and neovascular AMD were significantly higher in men than in women.

Age-specific 5-year incidences of early and late age-related maculopathy by sex are shown in Table 3. The incidence of

TABLE 2. Incidence of Early and Late ARM Lesions by Sex

	Men		Women		All Subjects	
	Population at Risk	Incidence *n* (%)	Population at Risk	Incidence *n* (%)	Population at Risk	Incidence *n* (%)
Early ARM	304	34 (11.2)	488	33 (6.8)	792	67 (8.5)
Pigmentary abnormalities	304	9 (3.0)	488	4 (0.8)*	792	13 (1.6)
Soft distinct and indistinct drusen	304	25 (8.2)	488	29 (5.9)	792	54 (6.8)
Late ARM	377	7 (1.9)	571	1 (0.2)**	948	8 (0.8)
Geographic atrophy	377	3 (0.8)	571	0 (0.0)*	948	3 (0.3)
Neovascular ARM	377	4 (1.1)	571	1 (0.2)*	948	5 (0.5)

** $P < 0.01$, men versus women.

early ARM significantly increased with advancing age in women. After adjustment for age, the incidence of early ARM was slightly but not significantly higher in men than in women (OR, 1.63; 95% CI, 0.98–2.49). The incidence of late ARM significantly increased with advancing age in men. After adjustment for age, men were found to have a significantly higher incidence of late ARM than were women (OR, 2.62; 95% CI, 1.18–5.82). The incidence of any ARM significantly increased with advancing age in all subjects.

The results of age and multivariate-adjusted logistic regression analyses of risk factors for the 5-year incidence of early and late ARM are shown in Table 4. After adjustment for age, habitual smoking was significantly associated with early and late ARM. The multivariate regression analysis showed that age and smoking were significantly associated with both early and late ARM.

DISCUSSION

To our knowledge, this is the first study to investigate the 5-year incidence and risk factors of ARM in Japan by using population-based cohort data. The results show that the overall 5-year incidence of early ARM was 8.5% and that of late ARM was 0.8%, and that both age and smoking were significantly associated with ARM.

Several prospective studies on the incidence of ARM have been conducted in various regions of the world.[15–18] The results of the present study can be compared with those in the Beaver Dam Eye Study[15] and the Blue Mountains Eye Study,[16] since our methodology and grading system were almost identical with those used in these earlier works. Our early and late ARM incidences were similar to the reported incidences of early and late ARM in the Beaver Dam Eye Study[15] (8.2% and 0.9% for early and late ARM, respectively) and the Blue Mountains Eye Study[16] (8.7% and 1.1% for early and late ARM, respectively). A slightly lower incidence of early and late ARM was found in our study compared with the Blue Mountains Eye Study.[16] This difference in ARM incidence among the three studies could be due to the differences in environmental exposure among the populations, to genetic factors, or perhaps to the differences in methodology among the three studies. In this study we used 45° fundus photographs to grade ARM. It is known that ARM, especially early ARM, is less likely to be detected by grading of fundus photographs than by grading of 30° fundus photographs. However, reliance on 45° fundus photographs theoretically could result in underestimation of the incidence of ARM by missing subtle early macular changes. This may be the reason for the lower incidence of early and late ARM observed in our study.

The present study, as well as the two previous studies,[15,16] found that the incidence of early ARM significantly increased with advancing age in women and that the incidence of late ARM significantly increased with advancing age in men. However, we found no such correlation between age and late ARM in women. This difference may have resulted from the relatively low incidence of late ARM among the women in our study.

We found a significantly higher incidence of late ARM among Japanese men than among Japanese women. We have already reported that early and late ARM are more prevalent among men than women in the representative Japanese community of Hisayama, using cross-sectional data from the Hisayama study.[9] Yuzawa et al.[19] have also reported that late ARM is more prevalent in men than in women in patients visiting ophthalmology departments in Japan. In contrast, ARM is more prevalent in women than in men in Western countries.[20,21] In the Beaver Dam[15] and Blue Mountains[16] eye studies, the incidence was slightly higher in women than in men for both early and late ARM. For late ARM, the incidence in women was double that in men in the Blue Mountains Eye Study.[16] The reason for this difference is not clear. However, smoking, which is known to be a major risk factor for ARM,[7,22,23] is likely to have contributed to the observed difference in the incidence of ARM, because, in Japan, habitual smoking is significantly more prevalent in men than in women.

The results of this study provide prospective evidence that cigarette smoking increases the risk of development of ARM. Compared with those who never smoked, those who had smoked in the past or were currently smoking had 2.2 times the risk of ARM, after adjustment for other potential risk fac-

TABLE 3. Age-Specific 5-Year Incidence of Early and Late ARM by Sex

	Men				Women				All Subjects	
Age (y)	Population at Risk	Early ARM *n* (%)	Population at Risk	Late ARM *n* (%)	Population at Risk	Early ARM *n* (%)	Population at Risk	Late ARM *n* (%)	Population at Risk	Any ARM *n* (%)
50–59	102	9 (8.8)	119	0 (0.0)	162	6 (3.7)	186	0 (0.0)	264	15 (5.7)
60–69	130	13 (10.0)	160	4 (2.5)	217	14 (6.5)	251	0 (0.0)	347	27 (7.8)
70–79	69	9 (13.0)	90	2 (2.2)	102	11 (10.8)	125	1 (0.8)	171	20 (11.7)
80+	3	0 (0.0)	8	1 (12.5)	7	1 (14.3)	9	0 (0.0)	10	1 (10.0)
Total	304	31 (10.2)	377	7 (1.9)	488	32 (6.6)	571	1 (0.2)	792	63 (8.0)

TABLE 4. Age and Multivariate-Adjusted ORs of Risk Factors for the 5-Year Incidence of Early and Late ARM

	Age-Adjusted		Multivariate-Adjusted	
Risk Factor	OR†	(95% CI)‡	OR†	(95% CI)‡
Age			1.04*	(1.01–1.07)
Sex (Men)	1.63	(0.98–2.49)		
Hypertension	1.08	(0.70–1.67)		
Diabetes	0.55	(0.25–1.23)		
Hyperlipidemia	1.04	(0.68–1.59)		
Smoking habit	2.22*	(1.14–4.33)	2.22*	(1.14–4.33)
Alcohol intake	1.25	(0.81–1.91)		
Body mass index	0.98	(0.91–1.05)		
White blood cells	0.97	(0.83–1.13)		

Multivariate OR is adjusted for age, sex, hypertension, diabetes, hyperlipidemia, smoking habit, alcohol intake, body mass index, and white blood cells, using the stepwise method.

* $P < 0.05$

† OR; odds ratio

‡ CI; confidence interval

tors. These findings are consistent with other cross-sectional and cohort data that showed that cigarette smoking is related to the development of ARM.[7,22–27]

This study had several limitations. First, our results could have been biased by the low response rate. Our data suggest that persons lost to follow-up were more likely at baseline to be slightly older, to have hypertension, and to have diabetes. As age is strongly associated with the prevalence of ARM, differential losses to follow-up due to differences in these characteristics could have resulted in an underestimation of the incidence of ARM in this population. However, there were no significant differences between the two groups in the presence of ARM or lifestyle habits. Although it is not possible to predict the magnitude of any such underestimation, we believe that it is not likely to be a major one. Second, drusen were defined as either indistinct or distinct drusen in our study, whereas they were defined as indistinct soft drusen in both the Beaver Dam[15] and Blue Mountains[16] eye studies. This distinction may be the reason for the differences in the incidence of early ARM among the three studies.

In conclusion, the results of this study suggest that the overall 5-year incidence of early ARM is 8.0% and that of late ARM is 0.8% in the general Japanese population and that higher age and smoking are relevant risk factors for early and late ARM in the Japanese.

References

1. Klein R, Wang Q, Klein BE, Moss SE, Meuer SM. The relationship of age-related maculopathy, cataract, and glaucoma to visual acuity. *Invest Ophthalmol Vis Sci.* 1995;36:182–191.
2. Munoz B, West SK, Rubin BS, et al. Causes of blindness and visual impairment in a population of older Americans: the Salisbury Eye Evaluation Study. *Arch Ophthalmol.* 2000;118:819–825.
3. Attebo K, Mitchell P, Smith W. Visual acuity and the causes of visual loss in Australia: The Blue Mountains Eye Study. *Ophthalmology.* 1996;103:357–364.
4. Mitchell P, Smith W, Wang JJ. Iris color, skin sun sensitivity, and age-related maculopathy: The Blue Mountains Eye Study. *Ophthalmology.* 1998;105:1359–1363.
5. Sperduto RD, Hiller R. Systemic hypertension and age-related maculopathy in the Framingham Study. *Arch Ophthalmol.* 1986; 104:216–219.
6. Vingerling JR, Dielemans I, Bots ML, et al. Age-related macular degeneration is associated with atherosclerosis: the Rotterdam Study. *Am J Epidemiol.* 1995;142:404–409.
7. Klein R, Klein BEK, Linton KLP, et al. The Beaver Dam Eye Study: the relation of age-related maculopathy to smoking. *Am J Epidemiol.* 1993;137:190–200.
8. Ritter LL, Klein R, Klein BEK, et al. Alcohol use and age-related maculopathy in the Beaver Dam Eye Study. *Am J Ophthalmol.* 1995;120:190–196.
9. Miyazaki M, Nakamura H, Kubo M, et al. Risk factors for age related maculopathy in a Japanese population: the Hisayama study. *Br J Ophthalmol.* 2003;87:469–472.
10. Ohmura T, Ueda K, Kiyohara Y, et al. Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. *Diabetologia.* 1993;36:1198–1203.
11. Klein R, Meuer SM, Moss SE, et al. Detection of drusen and early signs of age-related maculopathy using a nonmydriatic camera and a standard fundus camera. *Ophthalmology.* 1992;99:1686–1692.
12. Bird AC, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol.* 1995;39:367–374.
13. Klein R, Davis MD, Magli YL, et al. The Wisconsin age-related maculopathy grading system. *Ophthalmology.* 1991;98:1128–1134.
14. SAS Institute Inc.: *SAS/STAT User's Guide*. ver. 8. vol. 2. Cary, NC: SAS Institute Inc.; 1989:1247–2552.
15. Klein R, Klein BEK, Jensen SC, Meuer SM. The five-year incidence and progression of age-related maculopathy: The Beaver Dam Eye Study. *Ophthalmology.* 1997;104:7–21.
16. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: The Blue Mountains Eye Study. *Ophthalmology.* 2002;109:1092–1097.
17. Bressler NM, Munoz B, Maguire MG, et al. Five-year incidence and disappearance of drusen and retinal pigment epithelial abnormalities: Waterman Study. *Arch Ophthalmol.* 1195;113:301–308.
18. Sparrow JM, Dickson AJ, Duke AM, Thompson JR, Gibson JM, Rosenthal AR. Seven year follow-up of age-related maculopathy in an elderly British population. *Eye.* 1997;11:315–324.
19. Yuzawa M, Tamakoshi A, Kawamura T, et al. Report on the nationwide epidemiological survey of exudative age-related macular degeneration in Japan. *Int Ophthalmol.* 1997;21:1–3.
20. Mitchell P, Smith W, Attebo K, et al. Prevalence of age-related maculopathy in Australia: The Blue Mountains Eye Study. *Ophthalmology.* 1995;102:1450–1460.
21. Klein R, Rowland ML, Harris MI. Racial/ethnic differences in age-related maculopathy. Third National Health and Nutrition Examination Survey. *Ophthalmology.* 1995;102:371–381.
22. Christen WG, Glynn RJ, Manson JE, Ajani UA, Buring JE. A prospective study of cigarette smoking and risk of age-related macular degeneration in men. *JAMA.* 1996;276:1147–1151.
23. Seddon JM, Willett WC, Speizer FE, Hankinson SE. A prospective study of cigarette smoking and risk of age-related macular degeneration in women. *JAMA.* 1996;276:1141–1156.
24. Vingerling JR, Klaver CCW, Hofman A, et al. Age-related maculopathy. *Epidemiol Rev.* 1995;17:347–360.
25. Smith W, Michell P, Leeder SR. Smoking and age-related maculopathy: The Blue Mountain Eye Study. *Arch Ophthalmol.* 1996;114:1518–1523.
26. Age-related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration: a case-control study in the Age-related Eye Disease Study: AREDS report no. 3. *Ophthalmology.* 2000;107:2224–2232.
27. Smith W, Assink J, Klein R, et al. Risk factors for age-related macular degeneration: pooled findings from three continents. *Ophthalmology.* 2001;108:2224–2232.

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Secular trends in the incidence, mortality, and survival rate of gastric cancer in a general Japanese population: the Hisayama study

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Abstract

To examine secular trends in the incidence and mortality of gastric cancer in a Japanese community, Hisayama, we established three study-cohorts of Hisayama residents aged ≥40 years in 1961 (1637 subjects), 1974 (2054), and 1988 (2602). Each cohort was followed up for ten years. The age-standardized mortality from gastric cancer significantly decreased from 2.4 per 1000 person-years in the first cohort to 0.8 in the third cohort for men, and from 1.0 to 0.2, respectively, for women ($p < 0.01$ for trend in both sexes). The five-year survival rate after gastric cancer significantly improved from the first (32.6%) to the third cohort (73.0%, $p < 0.01$) for men and from 43.2% to 72.3% ($p < 0.05$), respectively, for women. The age-standardized incidence of cancer in men was not different among the cohorts (4.3 per 1000 person-years in the first, 5.0 in the second, and 4.9 in the third cohort), while it decreased significantly in women (2.0, 1.8, and 1.2, respectively, $p < 0.01$ for trend). In conclusion, our findings suggest that in a Japanese population, the mortality from gastric cancer declined during the past 40 years, due mainly to the improvement of survival in both sexes and a decrease in the incidence for women.

Introduction

In Japan, gastric cancer is one of the most common malignant neoplasms [1]. According to recorded vital statistics, the age-standardized mortality from gastric cancer among Japanese has declined conspicuously during the past 25 years [2, 3], although mortality from gastric cancer in Japan is still the highest in the world [2]. A mass screening program and advances in therapy for gastric cancer have been shown to have contributed to the decrease in the mortality rate [4–6]. However, it is not yet definite whether the incidence of gastric cancer actually declined during the same period.

There have been several reports from registration studies on secular changes in the incidence [1–3, 7, 8] and mortality [4, 5] of gastric cancer in Japan. However, the study designs may have had some limitations; they miss concealed cancers unless autopsy is inevitably carried out, the data are affected by the registration rate [9], and methods for case ascertainment are potentially biased by the secular improvement of diagnostic techniques.

The Hisayama study is a population-based cohort study of cardiovascular disease whose authors have established three study-cohorts at times corresponding to the remarkable lifestyle changes in Japan [10–12]. The most outstanding feature of this study is that causes of death in most deceased subjects were verified by autopsy. In the present study, we compared follow-up data of these cohorts and examined the trends in the incidence, mortality, and five-year survival rates of gastric cancer. We consider the design of this study to be a more accurate method for determining secular trends in cancer morbidity and mortality, and to provide useful evidence for the introduction of public health strategy for the prevention of gastric cancer.

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Subjects and methods

Study population

Hisayama Town is a suburban community adjacent to Fukuoka City, a metropolitan area on the third-largest island of Japan (Kyushu Island). The population of the town has been stable for 40 years (the annual variation rate is < 5%) [13] and has been shown to be representative of Japan as a whole based on data from the national census [10, 14]. We established three study-cohorts from Hisayama residents aged 40 years or older in 1961, 1974, and 1988 after health check-ups [10–12, 14]. In 1961, a total of 1658 subjects in that age group consented to participate in a health check-up (participation rate, 90.1%). After excluding seven subjects with a history of gastric cancer or gastrectomy prior to the health check-up and 14 subjects who died or moved out of town during the examination period, 1637 subjects were enrolled as the first cohort. In the same manner, we established a second cohort consisting of 2054 subjects from 2135 participants in the 1974 examination (participation rate, 81.2%), and a third cohort of 2602 subjects from 2742 participants in the 1988 examination (participation rate, 80.9%).

Follow-up survey

The cohorts have been undergoing longitudinal observations by annual health examinations. Health status was checked every year by mail or telephone for subjects who did not undergo a regular examination or who had moved out of town. In order to identify new occurrence of gastric cancer in the cohorts, we checked all of the records of the annual mass screenings for gastric cancer by barium X-ray examination, which started in Hisayama Town in 1964, and it covered approximately 40% of the target population. We also monitored radiographic and endoscopic study records and endoscopic biopsy records of the stomach at local clinics or general hospitals in and around Hisayama. Further, when a subject of each cohort died, an effort was made to obtain permission for autopsy from the family to clarify the concealed cancer. Autopsies were performed at the Department of Pathology of Kyushu University. During the 10-year follow-up period of each cohort, autopsy was carried out in 282 (80.6%) of 350 deaths in the first cohort, 307 (85.8%) of 358 deaths in the second cohort, and 302 (77.2%) of 391 deaths in the third cohort.

Cases of gastric cancer were confirmed by medical records, autopsy findings, or death certificates. Clinical diagnoses and causes of death were established by medical records and were corrected by autopsy findings when necessary. During the follow-up, only four subjects in the first cohort, one in the second cohort, and one in the third cohort were lost to follow-up, and first-ever gastric cancer occurred in 59, 76, and 76 subjects in each cohort, respectively. The early gastric cancer was defined as tumor invasion limited into mucosa or submucosa of the stomach, irrespective of the presence or absence of metastasis to other organs.

Risk factors

Recumbent blood pressures were measured at every examination, and hypertension was defined as ≥140/90 mmHg and/or a current use of antihypertensive agents. Glucose intolerance was defined by an oral glucose tolerance test in the subjects with glycosuria in 1961, by fasting and postprandial glucose concentrations in 1974, and by a 75-g oral glucose tolerance test in 1988, in addition to medical history of diabetes. Serum cholesterol levels were measured by the modified Zak–Henly method in 1961, by the Zurkowski method in 1974, and by the enzymatic method in 1988. Hypercholesterolemia was defined as total cholesterol ≥5.7 mmol/l. Obesity was defined as body mass index ≥25.0 kg/m^2. Information on antihypertensive treatment, alcohol intake, and smoking habits was obtained with the use of a standard questionnaire and was categorized as current habitual use or not. Subjects who reported smoking at least one cigarette per day were defined as current smokers, and subjects who reported consuming alcohol at least once a month were regarded as current drinkers.

Statistical analysis

The significance of risk factor trends was examined with the Cochran–Armitage test. The incidence and mortality rates of gastric cancer were calculated by the person-year method and adjusted for the age-distribution of the world standard population by the direct method. The differences in the incidence and mortality among three cohorts were tested using the Cox proportional hazards model [15] after adjusting for age. In cases of gastric cancer except for those first diagnosed at autopsy, the five-year survival curves were calculated and their differences among three cohorts were tested using the Cox proportional hazards model [15] after adjusting for age, too. In the calculation of the survival curves, only gastric cancer-related death was considered as the end point. The differences in the clinicopathological characteristics of cases with gastric cancer among three cohorts were examined with the chi-square test. All statistical analyses were performed using the SAS program package.

A *P*-value >0.05 was considered statistically significant in all analyses.

Results

We compared the prevalence of risk factors at the baseline examination among the three study cohorts by sex (Table 1). In both sexes, mean age and prevalence of glucose intolerance, hypercholesterolemia, and obesity increased progressively with time. The frequency of current smokers in both sexes and that of male drinkers linearly declined over the cohorts. In each cohort, the frequencies of current smokers and drinkers were much higher in men than in women. Table 2 compares the age-standardized mortality and incidence of gastric cancer among three cohorts during the ten-year follow-up period by sex. The age-standardized cancer mortality declined by 21% from 2.4 per 1000 person-years in the first cohort to 1.9 in the second cohort in men, and by 20% from 1.0 to 0.8, respectively, in women. It further steeply declined to 0.8 in men (by 58% of the second cohort, $p=0.009$ for trend), and 0.2 in women (75%, $p=0.001$ for trend) in the third cohort.

In men, the age-standardized incidence of gastric cancer did not significantly change from 4.3 per 1000 person-years in the first cohort to 4.9 in the third cohort. In contrast, the incidence for women declined by 10% from 2.0 in the first cohort to 1.8 in the second cohort, and it continued to decline to 1.2 in the third cohort, by 33% of the second cohort ($p=0.029$ for trend).

The age-specific incidence of gastric cancer for men is shown in Figure 1. The incidence increased with advancing age in all study-cohorts. The incidence in the subjects aged 70 years or over was higher in the second cohort than in other cohorts. The cancer incidence for women also increased with elevating age in the first cohort, but it consistently decreased from the first to the third cohort in the subjects aged 70 years or over (Figure 2).

The age-adjusted five-year survival curves are shown for men (Figure 3) and women (Figure 4). The 5-year

Table 1. Prevalence of risk factors at baseline among three Hisayama cohorts by sex

	Men				Women			
	1st cohort 1961 (n = 713)	2nd cohort 1974 (n = 866)	3rd cohort 1988 (n = 1070)	*p* For trend	1st cohort 1961 (n = 924)	2nd cohort 1974 (n = 1188)	3rd cohort 1988 (n = 1532)	*p* For trend
Age (years)	56 ± 11	57 ± 11	57 ± 12	0.006	57 ± 12	58 ± 12	59 ± 12	<0.001
Glucose intolerance (%)	12.2	14.6	34.0	<0.001	4.7	8.3	27.9	<0.001
Hypercholesterolemia (%)	3.2	12.4	27.0	<0.001	7.3	21.2	43.3	<0.001
Obesity (%)	7.5	11.9	24.5	<0.001	13.0	21.8	23.8	<0.001
Hypertension (%)	39.1	42.6	42.8	0.145	38.1	44.7	39.2	0.953
Current smoker (%)	74.6	72.1	49.7	<0.001	16.3	10.7	7.0	<0.001
Current drinker (%)	68.8	64.9	61.7	0.002	8.1	5.7	9.1	0.178

Obesity was defined as body mass index ≥25.0 kg/m^2. Hypercholesterolemia was defined as total cholesterol ≥5.7 mmol/l. Hypertension was defined as ≥140/90 mmHg and/or a current use of antihypertensive agents.

Table 2. Comparison of age-standardized mortality and incidence rates of gastric cancer during 10-year follow-up among three Hisayama cohorts by sex

	Men				Women			
	1st cohort 1961–1971 (n = 713)	2nd cohort 1974–1984 (n = 866)	3rd cohort 1988–1998 (n = 1070)	*p* For trend	1st cohort 1961–1971 (n = 924)	2nd cohort 1974–1984 (n = 1188)	3rd cohort 1988–1998 (*n* = 1532)	*p* For trend
Mortality								
Person-year	5947	7455	9364		7976	10,532	13,778	
Event, n	15	21	9		12	13	4	
Mortality rate	2.4	1.9	0.8*	0.009	1.0	0.8	0.2**	0.001
Incidence								
Person-year	5892	7351	9198		7940	10,479	13,706	
Event, n	28	49	54		21	27	22	
Incidence rate	4.3	5.0	4.9	0.818	2.0	1.8	1.2**	0.029

Mortality and incidence rate: per 1000 person-years. $^{**}p < 0.01$, $^{*}p < 0.05$, versus 1st cohort.

survival rate for men improved from the first (32.6%) to the second (51.4%) and further significantly improved from the second to third cohort (73.0%, $p < 0.01$). Among women, the five-year survival rate was not different between the first (43.2%) and second cohort (36.2%), but it significantly improved from the second to the third cohort (72.3%, $p < 0.05$). The difference in the survival rates between the sexes was not significant in any cohort.

Table 3 indicates clinicopathological findings in cases of gastric cancer in the three cohorts. The proportion of men increased from 57.1% in the first cohort to 71.1% in the third cohort. Among men, the mean age at the diagnosis of cancer was significantly higher in the second cohort than in the first cohort, while there was no difference in age between the second and third cohorts. The age at the diagnosis of cancer was not different among three cohorts in women. In regard to the location of cancer in the stomach, the proportion of cancers in the upper third of the stomach was not different among the three cohorts. The proportion of cancers in the middle third of the stomach increased from 18.6% in the first cohort to 35.7% in the second cohort, while that in the lower third of the stomach decreased oppositely from 65.1% to 48.6%, respectively.

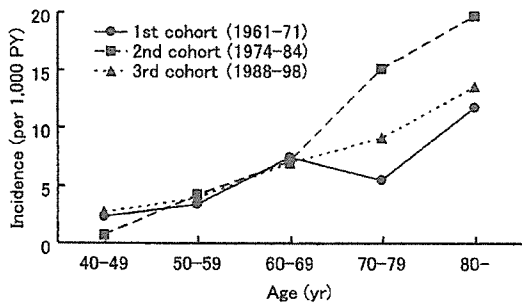

Fig. 1. The age-specific incidence of gastric cancer for men during ten-year follow-up of three Hisayama cohorts.

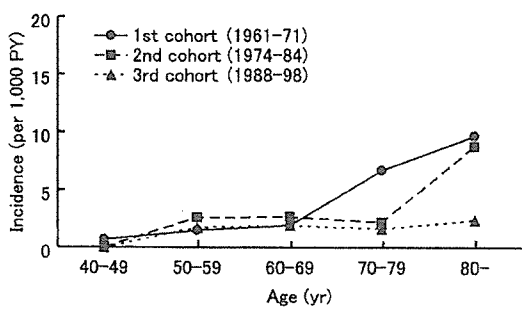

Fig. 2. The age-specific incidence of gastric cancer for women during ten-year follow-up of three Hisayama cohorts.

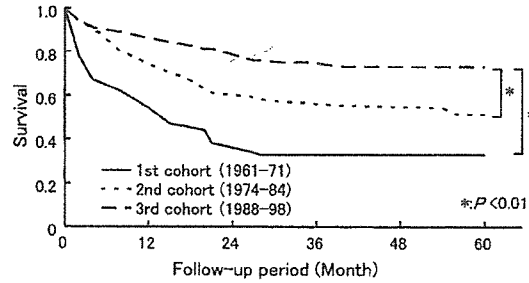

Fig. 3. Age-adjusted five-year survival curves of gastric cancer for men during ten-year follow-up in three Hisayama cohorts.

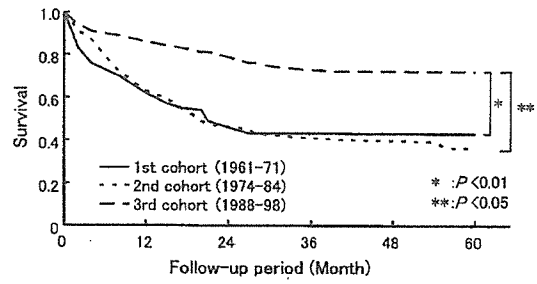

Fig. 4. Age-adjusted five-year survival curves of gastric cancer for women during ten-year follow-up in three Hisayama cohorts.

These changes were not observed between the second and third cohorts. The proportion of early gastric cancer significantly increased from 6.1% in the first cohort to 61.8% in the third cohort, and the proportion of cases with curative operation significantly increased from 53.1% to 84.2%, respectively. On the contrary, the proportion of concealed cancers first diagnosed at autopsy decreased from 18.4% in the first cohort to 3.9% in the third cohort.

Discussion

By comparing the incidence, mortality, and survival rates of gastric cancer among three cohorts established at different times in a Japanese community, we demonstrated that the mortality from this type of cancer declined slightly from the first to the second cohort, and further steeply declined from the second to the third cohort, due mainly to the improvement of survival rates for both sexes. The incidence of gastric cancer for women also decreased consistently from the first to the third cohort; however, the cancer incidence for men remained high and showed no apparent secular trend.

Previous registration studies in Japan have reported that the mortality and incidence of gastric cancer secularly declined in both men and women [2, 7]. In

Table 3. Clinicopathological characteristics of cases with gastric cancer in three Hisayama cohorts

	1st cohort (n = 49)	2nd cohort (n = 76)	3rd cohort (n = 76)
Man, n (%)	28 (57.1)	49 (64.5)	54 (71.1)
Mean age, M/F (years)	62.6/69.6	68.5*/67.9	66.2/69.1
Location			
Upper third, n (%)	7 (16.3)	11 (15.7)	12 (15.8)
Middle third, n (%)	8 (18.6)	25 (35.7)	27 (35.5)
Lower third, n (%)	28 (65.1)	34 (48.6)	37 (48.7)
Early cancer, n (%)	6 (6.1)	32** (42.1)	47**,† (61.8)
Curative operation, n (%)	26 (53.1)	55** (72.4)	64** (84.2)
Concealed case, n (%)	9 (18.4)	8 (10.5)	3 (3.9)

**$p < 0.01$, *$p < 0.05$ versus 1st cohort. †$p < 0.01$ versus 2nd cohort.
Concealed case: gastric cancer first diagnosed at autopsy.

our cohort, the incidence of gastric cancer in men remained unchanged during the past 40 years, while it decreased in women. This discrepancy between our study and the others may have been caused by a difference in environmental factors as well as in study populations and research method, such as that for ascertainment of cancer cases.

Based on the different results of the trend in the incidence of gastric cancer between the men and women included in our study, it could be hypothesized that risk factors for gastric cancer are different between the sexes. It is well known that *Helicobacter pylori* infection is one of the major risk factors for gastric cancer. However, our previous study showed that this association was confirmed only for men and not for women in the third cohort, although the prevalence of *Helicobacter pylori* infection has been shown to be high in both sexes (72% for men, 62% for women) [12]. The high prevalence of *Helicobacter pylori* infection in men, which was presumed to be true for other earlier cohorts, might have caused the high incidence of gastric cancer from the first to the third cohort. On the other hand, the declining trend in the incidence for women might reflect changes in cancer-related environmental factors rather than the effect of *Helicobacter pylori* infection. Kaminei *et al.* [16] reported the incidence of gastric cancer in the second generation of Japanese immigrants to the United States to be half that of the first generation. This observation also suggests that a decrease in the incidence of gastric cancer can be explained by changes in environmental factors. In particular, changes in foods and lifestyle may have contributed to the decrease in the incidence of gastric cancer in the women in our study. The frequency of smoking was low and decreased steadily from the first (16%) to the third cohort in women (7%), while smoking was maintained at high levels among men in the first (75%) and the second cohort (72%) and decreased to 50% in the third cohort, though the latter was still higher than that in Western populations [17]. The daily salt intake, which is also considered to be a risk factor for gastric cancer, steadily declined from 18 g per capita in 1965 to 10 g per capita in 1995 in the Hisayama population [18]. We cannot identify other risk factors that contributed to the decline in the incidence of gastric cancer in women. Further research into risk factors for gastric cancer is needed to clarify the reasons for changing patterns of gastric cancer incidence in the two sexes.

In our three cohorts, the incidence of gastric cancer among women, especially elderly women, decreased with time, and the incidence did not show an age-specific increasing trend in the third cohort. Since gastric cancer originates and develops due to long-term exposure to risk factors, especially in the elderly, this finding suggests that modifications to certain environmental factors have occurred in women. Changes in lifestyle for women, such as steadily decreasing trends in the frequency of smoking and the level of salt intake, might have led to the decrease in the incidence of gastric cancer in the elderly. In contrast, the incidence of gastric cancer for men increased with advancing age, and this phenomenon substantially unchanged in the three cohorts. The high frequency of smoking for men might have contributed to maintenance of high risk of gastric cancer in the elderly.

In the men and women of our study, mortality from gastric cancer steadily decreased, due mainly to the improved survival rates of cancer patients from the first to the third cohort. During this period, the proportion of concealed cancer decreased, while that of early cancer increased. These findings suggest that the survival for gastric cancer improved because of the early diagnosis of the cancer due to the promotion of mass screening with barium meal study and the advances in diagnostic and therapeutic procedures that occurred throughout Japan during this period.

Popularization of individual screening by endoscopy or radiography also contributed to the early diagnosis of gastric cancer.

Several limitations of our study should be discussed. First, since we did not perform a barium X-ray or endoscopic examination of the stomach in each subject at baseline examination, our study design could not exclude concealed cancer 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 was reported to be low (0.12%) by the nationwide mass screening in Japan [6]. Therefore, we believe that concealed cancers were rare at the time of the health check-up for each cohort, and that the influence of this bias is small. Second, there is a risk of time trend bias in our study, because the number of gastric cancers was small in each our cohorts. Nonetheless, we believe that the findings of our study represent the actual incidence and prognosis, since we performed this study using a highly accurate method for determining all gastric cancer cases. Finally, if patients of gastric cancer treated with endoscopic mucosal resection were not informed of the cancer, it was difficult to obtain information on gastric cancer from the subjects. Therefore, it is possible that the incidence in the third cohort, in which endoscopic mucosal resection had started, has been underestimated. However, we surveyed all the hospitals around Hisayama Town where town residents were usually admitted and where endoscopic procedures were being performed, and we believe, based on this effort, that the accuracy of our survey was high.

In conclusion, in a Japanese population, the mortality from gastric cancer declined from the 1960s to the 1990s, mainly as a result of the improvement of survival of gastric cancer for both sexes and a decrease in the cancer incidence for women. During this period, however, the incidence of gastric cancer for men remained unchanged. This is an important public health problem for Japanese, since their mortality from gastric cancer is still the highest in the world. In addition to eradication of *Helicobacter pylori*, further research into environmental and lifestyle factors related to gastric cancer is needed to establish preventive measures against this cancer.

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References

1. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (eds.) (1997) *Cancer incidence in Five Continents.* Lyon: International Agency for Research on Cancer.
2. Lambert R, Guilloux A, Oshima A, *et al.* (2002) Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. *Int J Cancer* **97**: 811–818.
3. Tominaga S (1987) Decreasing trend of stomach cancer in Japan. *Jpn J Cancer Res* **78**: 1–10.
4. Akoh JA, Macintyre IM (1992) Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. *Br J Surg* **79**: 293–299.
5. Nakamura K, Ueyama T, Yao, *et al.* (1992) Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* **70**: 1030–1037.
6. Hisamichi S (1989) Screening for gastric cancer. *World J Surg* **13**: 31–37.
7. The Research Group for Population-based Cancer Registration in Japan (1998) Cancer incidence in Japan, 1985–89: re-estimation based on data from eight population-based cancer registries. *Jpn J Clin Oncol* **28**: 54–67.
8. Hanai A, Kitagawa T, Ajika W, Tsukuma H, Oshima A (1998) Cancer incidence in Japan in 1990: estimates based on data from Population-based Cancer Registries. The Research Group for Population-based Cancer Registration in Japan. *Jpn J Clin Oncol* **28**: 450–453.
9. Schrijvers CT, Stronks K, van de Mheen DH, Coebergh JW, Mackenbach JP (1994) Validation of cancer prevalence data from a postal survey by comparison with cancer registry records. *Am J Epidemiol* **139**: 408–414.
10. Katsuki S (1966) Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* **21**: 64–89.
11. Ohmura T, Ueda K, Kiyohara Y, *et al.* (1993) 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.
12. Yamagata H, Kiyohara Y, Aoyagi K, *et al.* (2000) Impact of *Helicobacter pylori* infection on gastric cancer incidence in a general Japanese population: the Hisayama study. *Arch Intern Med* **160**: 1962–1968.
13. Ueda K, Omae T, Hirota Y, *et al.* (1981) Decreasing trend in incidence and mortality from stroke in Hisayama residents, Japan. *Stroke* **12**: 154–160.
14. Fujishima M, Kiyohara Y, Kato I, *et al.* (1996) Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes*, **45**(Suppl 3): S14–S16.
15. Cox DR (1972) Regression models and life-tables. *J R Stat Soc* **34**: 187–220.
16. Kamineni A, Williams MA, Schwartz SM, Cook LS, Weiss NS (1999) The incidence of gastric carcinoma in Asian migrants to the United States and their descendants. *Cancer Causes Control* **10**: 77–83.
17. Cavelaars AE, Kunst AE, Geurts JJ, *et al.* (2000) Educational differences in smoking: international comparison. *BMJ* **320**: 1102–1107.
18. Shirota T, Magome A, Miyamoto N, *et al.* (1999) Changes of nutrient intakes and food consumption structure over a 30-years period in Hisayama. *Bulletin of Nakamura Gakuen College & Nakamura Gakuen Junior College* **31**: 141–151.

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Relationship between obesity, glucose tolerance, and periodontal disease in Japanese women: the Hisayama study

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Background: Recent studies have reported a relationship between obesity and periodontal disease. Obesity is the strongest risk factor for type 2 diabetes, which is, in turn, a risk factor for periodontal disease. An oral glucose tolerance test is necessary to diagnose diabetes; however, no study has examined the relationship between obesity and periodontal disease by taking oral glucose tolerance test results into consideration.

Methods: In all, 584 Japanese women aged between 40 and 79 years old, with at least 10 teeth, underwent health examinations. Body mass index, waist–hip ratio, body fat, and oral glucose tolerance test results were used as independent variables with known risk factors for periodontal disease. Mean probing pocket depth and mean attachment loss were used as the dependent variables.

Results: In all of the analyses, body mass index, body fat, and waist–hip ratio were significantly associated with the highest quintile of mean probing pocket depth, even when adjusted for oral glucose tolerance test results. In the multivariate analysis, the subjects with the highest quartile of body mass index had a significantly higher odds ratio (OR) for the highest quintile of mean probing pocket depth [OR, 4.3; 95% confidence interval (CI), 2.1–8.9; $p < 0.001$], whereas neither impaired glucose tolerance nor diabetes were significantly associated with deep pockets. The relationships between the obesity indexes and mean attachment loss did not reach statistical significance.

Conclusion: Obesity was associated with deep pockets in Japanese women, even after adjusting for oral glucose tolerance test.

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Obesity, which is increasing worldwide, is a major risk factor for adult diseases such as type 2 diabetes, hyperlipemia, hypertension, cholelithiasis, arteriosclerosis, and cardiovascular and cerebrovascular disease (1). Of these disorders, the risk of type 2 diabetes is increased most by obesity, which reduces the glucose tolerance status (1, 2). The results of a Japanese national survey conducted in 1997 revealed that 53% of Japanese with diabetic conditions had previously been obese (body mass index ≥ 26.4) (3). Recent studies have reported that obesity, especially upper-body obesity, is significantly associated with probing pocket depth in the Japanese population (4–6). In the Third National Health and Nutrition Examination Survey (NHANES III), there was a significant association