後藤田　貴也	メタボリックシンドロームの遺伝的素因	最新医学	60 巻 1 号	22-29	最新医学社
Yamamoto A Harada-Shiba M Endo M Kusakabe N Tanioka T Kato H Shoji T	The effect of ezetimibe on serum lipids and lipoproteins in patients with homozygous familial hypercholesterolemia undergoing LDL-apheresis therapy	Atherosclerosis			in Press
Umeda M Harada-Shiba M Uchida K Nakayama Y	Photo-Control of the polyplexen formation between DNA and photo-cation eneratable water-soluble polymers	Current Drug Delivery	2	207-214	2005
Nakayama Y Masuda T Nagaishi M Hayashi M Ohira M Harada-Shiba M	High performance gene delivery polymeric vector: nano-structured cationic star polymers (star vectors)	Current Drug Delivery.	2	53-57	2005
槇野久士 斯波真理子	LDL アフェレーシス　一効果と限界—	The Lipid	17	49-54	2006
斯波真理子	ナノテクノロジー（ナノ DDS）を用いた動脈硬化性病変の治療・予防	分子心血管病	7	57-62	2006
斯波真理子	ARH ノックアウトマウス	The Lipid	16	316-322	2005
小林淳二、馬渕　宏	メタボリックシンドロームと動脈硬化性疾患診療ガイドライン	老年医学	43	751～758	2005
小林淳二、馬渕　宏	メタボリックシンドロームの高脂血症療法は？	肥満と糖尿病	4	703～705	2005
小林淳二、馬渕　宏	フィブラートの EBM	Progress in Medicine	25	2969~2972	2005
Kaneshi T, Yoshida T, Ohshiro T, Nagasaki N, Asato Y, Ohta T	Birth Weight and Risk Factors for Cardiovascular Diseases in Japanese Schoolchildren	Pediatr Int (in press)			

Sone H, Tanaka S, Ishibashi S, Yamasaki Y, Oikawa S, Ito H, Saito Y, Ohashi Y, Akanuma Y, Yamada N (The Japan Diabetes Complications Study Group)	The new worldwide definition of metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitions: Additional analysis from the Japan Diabetes Complications Study.	Diabetes Care	29	145-147	2006
Shinozaki S, Itabashi N, Rokkaku K, Ichiki K, Nagasaka S, Okada K, Fujimoto M, Ohtsuki M, Ishibashi S	Diabetic lipemia with eruptive xanthomatosis in a lean young female with apolipoprotein E4/4.	Diabetes Res Clin Pract	70	183-192	2005
Sone H, Mizuno S, Fujii H, Yoshimura Y, Yamasaki Y, Ishibashi S, Katayama S, Saito Y, Ito H, Ohashi Y, Akanuma Y, Yamada N	Japan Diabetes Complications Study: Is the diagnosis of metabolic syndrome useful for predicting cardiovascular disease in asian diabetic patients? Analysis from the Japan Diabetes Complications Study.	Diabetes Care	28	1463-1471	2005
Hayashi Y, Nagasaka S, Takahashi N, Kusaka I, Ishibashi S, Numao S, Lee DJ, Taki Y, Ogata H, Tokuyama K, Tanaka K	A single bout of exercise at higher intensity enhances glucose effectiveness in sedentary men.	J Clin Endocinol Metab	90	4035-4040	2005
Yamaguchi M, Matsumoto F, Bujo H,Shibasaki M, Takahashi K,Yoshimoto S, Ichinose M, Saito Y.	Revascularization determines volume retention and gene expression by fat grafts in mice.	Exp Biol Med (Maywood).	230(10)	742-8	2005

Ito M, Bujo H, Takahashi K, Arai T, Tanaka I,Saito Y.	Implantation of primary cultured adipocytes that secrete insulin modifies blood glucose levels in diabetic mice.	Diabetologia.	48(8)	1614-20	2005
Seki N, Bujo H, Jiang M, Tanaga K, Takahashi K, Yagui K, Hashimoto N, Schneider WJ, Saito Y.	LRP1B is a negative modulator of increased migration activity of intimal smooth muscle cells from rabbit aortic plaques.	Biochem Biophys Res Commun.	331(4)	964-70	2005
Fujita Y, Ezura Y, Bujo H,Nakajima T, Takahashi K,Kamimura K, Iino Y,Katayama Y, Saito Y,Emi M.	Association of nucleotide variations in the apolipoprotein B48 receptor gene (APOB48R) with hypercholesterolemia.	J Hum Genet.	50(4)	203-9	2005
Miyazawa-Hoshimoto S, Takahashi K,Bujo H,Hashimoto N, Yagui K,Saito Y.	Roles of degree of fat deposition and its localization on VEGF expression in adipocytes.	Am J Physiol Endocrinol Metab.	288(6)	E1128-36	2005
Seki N, Bujo H, Jiang M,Shibasaki M, Takahashi K, Hashimoto N, Saito Y.	A potent activator of PPARalpha and gamma reduces the vascular cell recruitment and inhibits the intimal thickning in hypercholesterolemic rabbits.	Atheroscleros is.	178(1)	1 － 7	2005
Hayashi T, Iguchi A et al.他３名	A. Selective iNOS inhibitor, ONO1714 successfully retards the development of high-cholesterol diet induced atherosclerosis by novel mechanism.	Atherosclerosi s	In press		
Hayashi T, Iguchi A, Ignarro LJ, et al.他３名	. l-Citrulline and l-arginine supplementation retards the progression of high-cholesterol-diet-induced atherosclerosis in rabbits.	Proc Natl Acad Sci U S A	102	13681-6	2005
Hayashi T, Nomura H, Iguchi A et al.	The treadmill exercise- tolerance test is useful for the prediction and prevention of ischemic coronary events in elderly diabetics.	J Diabetes Complications	19	264-268	2005

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

The Hisayama Study

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

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

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

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

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

Diabetes Care 28:789–794, 2005

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

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

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

RESEARCH DESIGN AND METHODS

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

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

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

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

Abbreviations: FPG, fasting plasma glucose.

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

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

Follow-up survey

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

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

Laboratory testing and risk factor measurement

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

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

Statistical analysis

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

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

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

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

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

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

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

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

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

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

In this study, the age-adjusted inci-

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

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

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

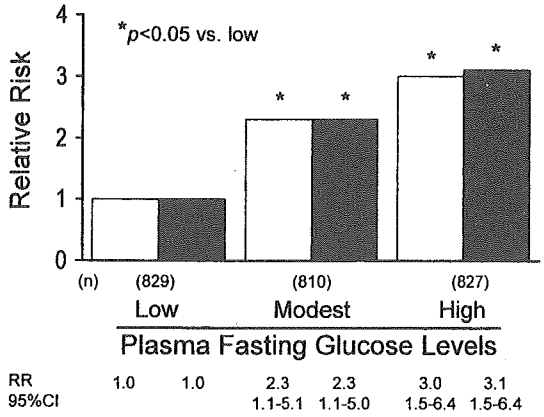

Figure 1—*Age- and sex-adjusted (□) and multivariate-adjusted (■) RR of gastric cancer of the modest-FPG (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group. In the multivariate analysis, the RR is adjusted for age, sex, BMI, serum cholesterol,* H.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

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

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

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

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

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

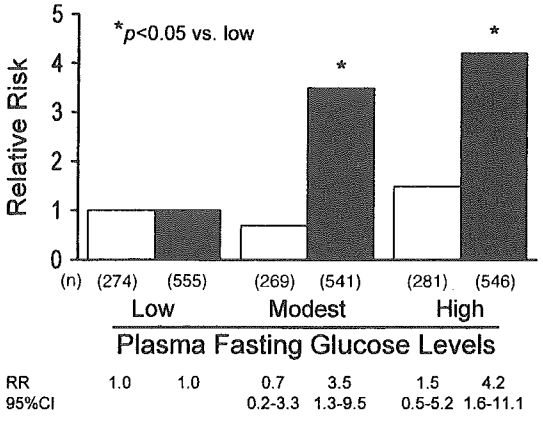

Figure 2—*Age- and sex-adjusted RR of gastric cancer of the modest (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group under stratification by* H. pylori *status.* □, H. pylori *seronegative;* ■, H. pylori *seropositive.*

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

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

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

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

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

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

References

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

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

Reprinted from JOURNAL OF NEUROLOGY, NEUROSURGERY AND PSYCHIATRY, March 2005, Vol 76, p 368-372

PAPER

Ten year recurrence after first ever stroke in a Japanese community: the Hisayama study

J Hata, Y Tanizaki, Y Kiyohara, I Kato, M Kubo, K Tanaka, K Okubo, H Nakamura, Y Oishi, S Ibayashi, M Iida

J Neurol Neurosurg Psychiatry 2005;**76**:368–372. doi: 10.1136/jnnp.2004.038166

See end of article for authors' affiliations

Correspondence to: Dr Jun Hata, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1 Higashi-ku, Fukuoka 812-8582, Japan; junhata@intmed2.med.kyushu-u.ac.jp

Received 30 January 2004
In revised form 26 June 2004
Accepted 11 July 2004

Background: Very few population based cohort studies have focused on the long term recurrence of stroke.
Objective: To examine 10 year cumulative recurrence rates for stroke in a Japanese cohort according to pathological type and clinical subtype of brain infarction.
Methods: During a 32 year follow up of 1621 subjects ≥40 years of age, 410 developed first ever stroke. These were followed up prospectively for 10 years after stroke onset.
Results: During follow up, 108 (26%) experienced recurrent stroke. The cumulative recurrence rates were 35.3% at five years and 51.3% at 10 years. The 10 year recurrence rates of subarachnoid haemorrhage (SAH), brain haemorrhage, and brain infarction were 70.0%, 55.6%, and 49.7%, respectively; the difference between SAH and brain infarction was significant ($p=0.004$). Most recurrent episodes after SAH or brain haemorrhage happened within a year after the index stroke, whereas recurrence of brain infarction increased consistently throughout the observation period. Cardioembolic stroke had a higher recurrence rate (75.2%) than lacunar infarction (46.8%) ($p=0.049$). The 10 year risk of stroke recurrence increased with age after lacunar or atherothrombotic brain infarction, but not after the other types or subtypes. After atherothrombotic brain infarction, cardioembolic stroke, or SAH, the type and subtype of most recurrent strokes were the same as for the index stroke, but recurrence after lacunar infarction or brain haemorrhage showed divergent patterns.
Conclusions: Japanese people have higher recurrence rates of stroke than other populations. Recurrence rate after a first brain infarct increases consistently through the next 10 years.

Japanese people have high rates of morbidity and mortality from stroke.[1] Among stroke survivors, recurrence is common, resulting in cumulative disability and cognitive dysfunction.[2] Consequently, precise information is needed on the long term rates and determinants of recurrence after first stroke, so that clinical trials can be designed and health care policies for primary and secondary stroke prevention can be established. Most studies on stroke recurrence, reported mainly from Western countries, have been based on stroke registries[3–11] or on series of patients referred to hospitals.[12 13] A truly representative assessment of stroke recurrence in a community would require a prospective cohort of a defined population and an exhaustive follow up system. The Framingham study is the only cohort based examination of both initial and recurrent stroke, but it refers to the recurrence of thrombotic brain infarction only.[14] Stroke is divided into several pathological types. Among them, brain infarction is further classified into several clinical subtypes.[15–17] Very few studies, however, have accurately defined types and subtypes while also evaluating the long term risk of stroke recurrence.[3]

Since 1961, we have been carrying out a prospective cohort study of cardiovascular disease in the town of Hisayama, Japan.[18 19] The most outstanding features of this study are that the causes of death were verified by necropsy and that most of the stroke patients were examined morphologically at necropsy or, before death, by brain imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI). Our aim in this study was to estimate 10 year cumulative recurrence rates after first ever stroke in the community of Hisayama, using data stratified by sex, age, stroke type, and, in cases of brain infarction, the clinical subtype.

METHODS

Subjects and follow up surveys

In 1961, we carried out a screening examination among Hisayama residents and established a cohort consisting of 1621 stroke-free subjects aged ≥40 years (88.1% of the total population in this age range). These subjects were then followed up for 32 years, from 1 November 1961 to 31 October 1993. A detailed description of the study methods has been published previously.[18 19] In brief, we collected information about new cardiovascular events through a daily monitoring system established by the study team, local practitioners, and the town government. When we suspected a patient was having a new neurological symptom or a new deterioration of an already existing symptom, one of the physicians participating in the study would carefully evaluate the subject and try to obtain information by further diagnostic examinations, including lumbar puncture, cerebral angiography, or recent brain CT or MRI. During the 32 year period, all but two subjects were followed up and 1063 subjects died. Of those who died, 861 (81.0%) underwent necropsy.

The study was conducted with the approval of the human ethics review committee of Kyushu University Graduate School of Medical Sciences.

First ever stroke

Stroke, defined as the sudden onset of a non-convulsive and focal neurological deficit persisting for over 24 hours, was classified into four pathological types: brain infarction, brain haemorrhage, subarachnoid haemorrhage, and undetermined. Brain infarction was further divided into four clinical subtypes: lacunar infarction, atherothrombotic brain

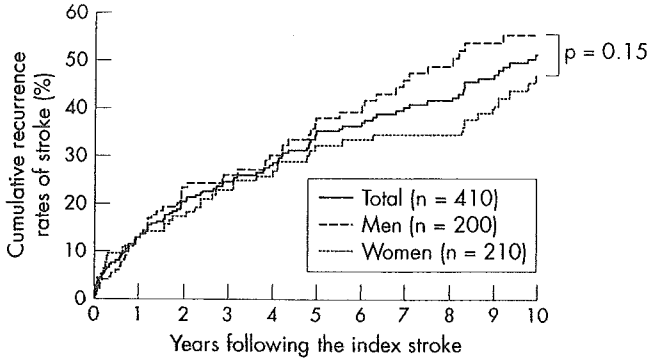

Figure 1 Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects and for all subjects divided by sex. Deaths without stroke recurrence were censored.

infarction, cardioembolic stroke, and undetermined. These types and subtypes were defined on the basis of the *Classification of Cerebrovascular Disease III* proposed by the National Institute of Neurological Disorders and Stroke (USA).[15] The subtypes of ischaemic stroke were classified by TOAST (trial of Org 10172 in acute stroke treatment)[16] and by the Cerebral Embolism Task Force.[17] A detailed method of classifying stroke has been published previously.[19] The diagnosis and classification of stroke in our study were based on clinical history, neurological examination, all available clinical information (including brain CT or MRI), and necropsy findings.

During the 32 year follow up, we identified 410 first ever stroke events (200 men and 210 women, mean (SD) age, 73.9 (10.1) years), and divided them into 298 cases of brain infarction, 73 of brain haemorrhage, 35 of subarachnoid haemorrhage, and four undetermined. The cases of brain infarction by subtype consisted of 167 lacunar infarcts, 62 atherothrombotic brain infarcts, 56 cardioembolic strokes, and 13 undetermined.

Recurrent stroke

The definition of recurrent stroke was the same as that of index stroke, but with an additional criterion: there had to be either a new focal neurological deficit or a new deterioration of a previous deficit that was not attributed to brain oedema, haemorrhagic transformation after ischaemia, intercurrent illness, or iatrogenesis. This definition included recurrence in the early stage after the preceding stroke or recurrence in the same vascular territory as the preceding stroke.

We followed up the 410 patients with index stroke from the time of stroke onset until death or 31 August 2003. Under those conditions, all patients completed the follow up period. In the 10 years after the index stroke, 108 patients developed recurrent stroke. Of these, 88 had one recurrent stroke, 13 had two, six had three, and one had four. However, the end point of this study for each subject was the first recurrence.

Morphological evaluation

Brain imaging, including CT or MRI, was carried out in 153 (37%) of the 410 subjects with index stroke and in 43 (40%) of the 108 subjects with recurrent stroke. Necropsy findings were available in 332 (84%) of the 394 deceased stroke patients. As a result, morphological evaluation, including brain imaging or necropsy, was undertaken in 376 (92%) of the index stroke patients and 102 (94%) of the recurrent stroke patients until 31 August 2003.

Because we began collecting data on stroke subjects in 1961, imaging examinations of the brain and heart were non-existent in the early study period. However, we compensated

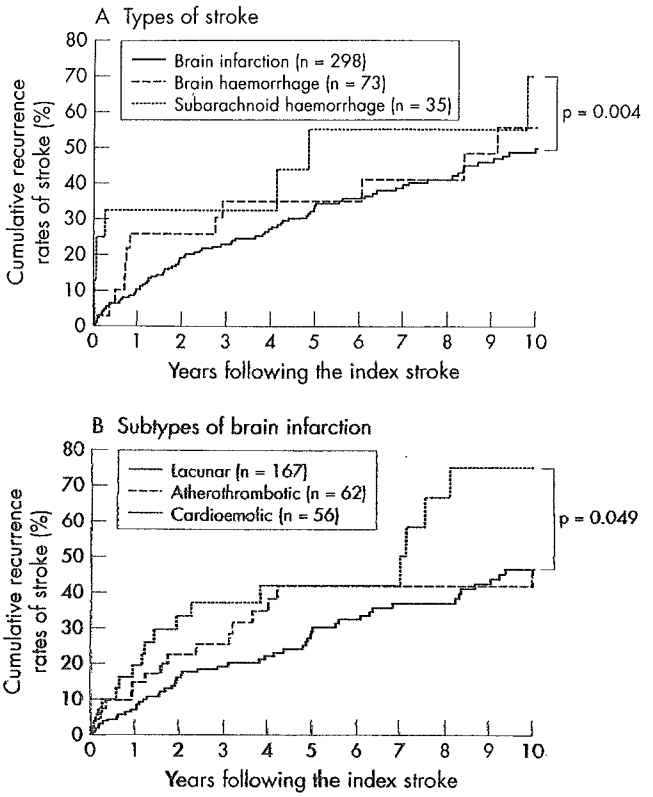

Figure 2 Kaplan–Meier estimates of cumulative recurrence rates of stroke according to stroke type (A) and, in cases of brain infarction, the subtype (B). Deaths without stroke recurrence were censored.

for this disadvantage by carrying out necropsy examinations on the vast majority of deceased patients. We reviewed the brains to evaluate the site, size, and pathological features of the stroke. We also investigated the heart and major vessels in detail—including the aorta, carotids, vertebrobasilar arteries, and the circle of Willis—in order to identify atherothrombotic stenotic lesions and embolic sources. In cases where the necropsy was carried out a long time after stroke onset, it was important to distinguish brain haemorrhage from brain infarction with haemorrhagic transformation. The latter was usually the result of a cardioembolic mechanism. When an infarcted area was surrounded by deposition of haemosiderin—with either no or mild atherosclerosis of the responsible artery, and given the presence of the embolic source—we considered the stroke lesion to be a brain infarct with haemorrhagic transformation. An old lesion that looked like a slit was considered to indicate a brain haemorrhage, especially if found in the basal ganglia or thalamus.

To classify the subtypes of brain infarction, we considered important the size and location of the infarcted area, the presence of stenosis or occlusion of a responsible cerebral artery, and the embolic source, in addition to clinical information including the disease course. Where multiple asymptomatic infarctions were present, we considered an infarct to be the lesion responsible for the stroke when it was most closely in accord with the neurological findings and disease course in the acute period of the stroke. The criteria for diagnosing brain infarction subtypes were given in full detail in our previous report.[19] When sufficient clinical and morphological information was obtained, a diagnosis of subtype was defined as "definite"; on the other hand, when either type of information was insufficient, the diagnostic level was defined as "probable." Among 298 cases of brain infarction, 272 were definite and 26 probable. In this study,

we present the data on the definite and probable cases together, as these combined data were almost identical to the data for definite cases only.

Statistical analysis

SAS software (version 6.12) was used for statistical analysis. The cumulative recurrence rates of stroke and the 95% confidence intervals (CI) were estimated by the Kaplan–Meier product limit method. The Cox proportional hazards model was used to test differences in recurrence rates as well as to estimate relative risks (RR) and 95% CIs of stroke recurrence.

RESULTS

Recurrence rates of stroke

Figure 1 shows the Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects and for all subjects divided by sex. The recurrence rates (95% CI) at 1, 5, and 10 years were 12.8% (8.9% to 16.6%), 35.3% (29.0% to 41.5%), and 51.3% (43.8% to 58.9%), respectively, for all subjects. For men, these rates were 12.9% (7.3% to 18.5%), 38.1% (28.9% to 47.2%), and 55.6% (44.9% to 66.4%); for women the rates were 12.5% (7.3% to 17.6%), 32.3% (23.8% to 40.9%), and 47.1% (36.5% to 57.6%). The recurrence rates were slightly higher for men than for women, but the overall difference was not statistically significant ($p = 0.15$).

Figure 2, panel A, shows cumulative recurrence rates of stroke by type of index stroke. The recurrence rates at 1, 5, and 10 years were 10.0% (6.3% to 13.8%), 34.1% (27.3% to 40.9%), and 49.7% (41.4% to 57.9%) after brain infarction; 25.6% (9.0% to 42.2%), 34.9% (16.0% to 53.8%), and 55.6% (32.2% to 79.1%) after brain haemorrhage; and 32.5% (10.3% to 54.6%), 55.0% (25.6% to 84.4%), and 70.0% (39.0% to 100%) after subarachnoid haemorrhage, respectively. The 10 year recurrence rate of subarachnoid haemorrhage was significantly higher than that of brain infarction (RR = 2.89 (95% CI, 1.40 to 5.97); $p = 0.004$). Also, brain haemorrhage recurred at a slightly higher rate than brain infarction, but the difference was not statistically significant ($p = 0.52$). Annual recurrence rates after brain infarction were about 10% per year in the first two years and consistently about 4% per year afterward. On the other hand, 58.3% of recurrent episodes took place within a year after brain haemorrhage, and 66.7% within three months after subarachnoid haemorrhage.

Figure 2, panel B, shows the cumulative recurrence rates of stroke by clinical subtype of brain infarction. The recurrence rates at 1, 5, and 10 years were 7.2% (3.1% to 11.2%), 30.4% (22.1% to 38.7%), and 46.8% (36.6% to 56.9%) after lacunar infarction; 14.8% (4.5% to 25.0%), 42.0% (25.5% to 58.5%), and 46.9% (29.2% to 64.5%) after atherothrombotic brain infarction; and 19.6% (6.3% to 32.8%), 42.2% (23.8% to 60.6%), and 75.2% (52.6% to 97.8%) after cardioembolic stroke, respectively. Cardioembolic stroke had a significantly higher risk of 10 year recurrence than lacunar infarction (RR = 1.76 (95% CI, 1.00 to 3.11); $p = 0.049$). The recurrence rate of atherothrombotic brain infarction was slightly higher than that of lacunar infarction, but the difference was not statistically significant ($p = 0.59$).

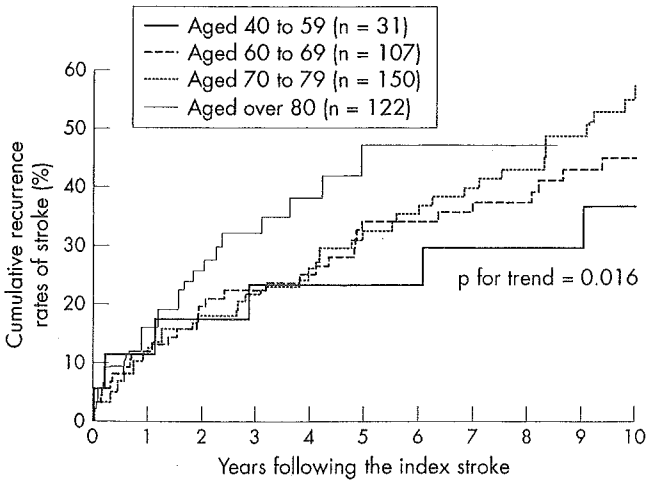

Figure 3 Kaplan–Meier estimates of cumulative recurrence rates of stroke for all subjects divided by age. Deaths without stroke recurrence were censored.

Figure 3 shows the cumulative recurrence rates of stroke by age. The 10 year risk of stroke recurrence was lowest in the youngest age group (40 to 59 years) and increased with age. Table 1 shows the relative risks of stroke recurrence among age groups during 10 years for each type and subtype of index stroke. The 10 year risk of stroke recurrence after brain infarction was lowest in the youngest age group and increased with age. For brain haemorrhage or subarachnoid haemorrhage, on the other hand, there was no significant relation between age and recurrence rates. Among the subtypes of brain infarction, the 10 year risk of recurrence after lacunar and atherothrombotic brain infarction was lowest in the youngest age group and increased with age, whereas for cardioembolic stroke there was no significant relation between age and recurrence rates.

Patterns of stroke recurrence

To evaluate patterns of stroke recurrence, table 2 shows the numbers and frequencies of first recurrent stroke by pathological types and clinical subtypes according to the type of index stroke. Most recurrent strokes after atherothrombotic brain infarction, cardioembolic stroke, or subarachnoid haemorrhage were the same type or subtype as the index stroke. On the other hand, recurrence after lacunar infarction or brain haemorrhage showed divergent patterns. The 51 patients who had recurrent stroke after lacunar infarction were divided as follows: 18 cases (35%) had a second lacunar infarction, 16 (31%) had atherothrombotic brain infarction, nine (18%) had brain haemorrhage, and six (12%) had cardioembolic stroke. Among the 12 recurrent cases of brain haemorrhage, seven (58%) had a second brain haemorrhage, three (25%) had lacunar infarction, and two (17%) had atherothrombotic or cardioembolic infarction.

DISCUSSION

One of the strengths of our study is that we investigated almost all stroke events occurring in a community based prospective cohort. Our study design eliminated the selection bias encountered in stroke registries or in series of hospital inpatients. Another strength is that recurrence rates were estimated up to 10 years after a subject's first ever stroke.

Recurrence rates of stroke

Three previous reports from stroke registries in Australia[3] and Britain[4 5] have reported five year cumulative stroke recurrence rates of 16.6% to 29.5%. In comparison, our study's five year cumulative stroke recurrence rate was 35.3%. There might be several reasons for this difference. First, there was a difference in methodology. The studies of the other three stroke registries all used a single set of criteria, which excluded vascular events occurring in the first 21 days after the index stroke unless such an event was clearly in a different vascular territory.[3–5] On the other hand, our study excluded neither early recurrence (10 cases within 21 days) nor recurrence in the same vascular territory. Second, race might greatly influence stroke recurrence. In our study,

Table 1 Relative risks and 95% confidence intervals of stroke recurrence during 10 years by age in each type or subtype of index stroke

	Age group (years)				
	40 to 59	60 to 69	70 to 79	80 and over	p Value
Index stroke	RR	RR (95% CI)	RR (95% CI)	RR (95% CI)	for trend
All types of stroke	1.0	1.3 (0.5 to 3.0)	1.6 (0.7 to 3.8)	2.2 (0.9 to 5.4)	0.016
Brain infarction	1.0	2.0 (0.6 to 6.5)	2.5 (0.7 to 8.1)	3.9 (1.1 to 13.1)	0.002
Lacunar infarction	1.0	2.2 (0.5 to 9.4)	2.6 (0.6 to 11.1)	4.8 (1.0 to 22.2)	0.022
Atherothrombotic brain infarction	1.0 *		1.8 (0.4 to 7.5)	4.7 (1.2 to 18.6)	0.001
Cardioembolic stroke	1.0	0.8 (0.1 to 7.3)	1.4 (0.2 to 12.3)	0.4 (0.0 to 4.1)	0.51
Brain haemorrhage	1.0	0.6 (0.0 to 6.3)	1.2 (0.2 to 10.3)	2.1 (0.2 to 24.3)	0.71
Subarachnoid haemorrhage	1.0	1.0 (0.2 to 6.0)	0.7 (0.1 to 4.4)	0.0	0.60

*Two age groups (40 to 59 and 60 to 69) were combined, as there were no recurrences after atherothrombotic brain infarction in the 40 to 59 age group.
CI, confidence interval; RR, relative risk.

haemorrhagic stroke—including brain haemorrhage and subarachnoid haemorrhage—recurred at higher rates than brain infarction, and the proportion of haemorrhagic stroke (26%) among all types was higher than those found in the three registries in Western countries (14% to 19%).[3–5] In addition, as Asians, including Japanese, have a higher stroke incidence than Europids,[1] they might also have higher rates of stroke recurrence.

In our study, most recurrent episodes occurred within a year after the index haemorrhagic stroke. This may indicate the importance of controlling risk factors and of treating the patient to prevent recurrence without delay in the first days and months after the onset of haemorrhagic stroke. On the other hand, cumulative recurrence rates after brain infarction, especially lacunar infarction, increased steadily during our 10 year study period. The Oxfordshire Community Stroke Project[6] also showed that the recurrence rate after lacunar infarction was low and almost constant throughout the follow up period. Arteriosclerosis, which is thought to progress consistently for a long period, may be related to recurrent thrombotic infarction. Thus careful observation and adequate treatment to prevent recurrence are needed for a long time after brain infarction.

Several studies have focused on the relations between brain infarction subtypes and the risks of recurrent stroke,[3 7–10 12] but their findings are equivocal. Some of those studies have claimed that the subtype of brain infarction is not a predictor of long term recurrence,[3 7 8] while others showed that the highest risk of recurrence is with atherothrombotic brain infarction.[9 10 12] In our study, cardioembolic stroke had the highest risk of recurrence among the three major subtypes of brain infarction. This is probably attributable to our inclusion of early recurrent episodes, which were often observed after cardioembolic stroke.[20 21]

In some studies,[3 11] aging was found to be a predictor of stroke recurrence. In the present study, the risk of recurrence after first ever lacunar or atherothrombotic brain infarction was lowest in the youngest age group and then increased with age. Aging would accelerate atherosclerotic changes in major cerebral arteries and arteriolosclerotic changes in penetrating arteries, thus increasing the risk of recurrent stroke.

Patterns of stroke recurrence

In the present study, the types or subtypes of most recurrent strokes after atherothrombotic brain infarction, cardioembolic stroke, or subarachnoid haemorrhage were the same as those of the index stroke. On the other hand, recurrence after lacunar infarction or brain haemorrhage showed divergent patterns. This finding was also emphasised in some previous reports.[4 13]

Several aetiological mechanisms for lacunar infarction have been proposed[22–24]: lipohyalinosis or microatheroma in a penetrating artery; branch-atheromatous disease, which is located in basilar or middle cerebral arteries and occludes the origins of one or more penetrating arteries; and microembolism from carotid or cardiac disease. These multifactorial aetiologies would support divergence in the type and subtype of recurrent stroke after lacunar infarction. Our findings denote the importance of evaluation to detect any large vessel disease or embolic source, even in patients with lacunar infarction.

Table 2 The numbers and frequencies of first recurrent stroke by pathological types and clinical subtypes according to type of index stroke

	Type or subtype of recurrent stroke								
		Subtype of BI							
Type or subtype of index stroke	All BI	LA	AT	CE	UND-BI	BH	SAH	UND	Total
Brain infarction	74 (85%)					10 (11%)	–	3 (3%)	87 (100%)
Lacunar infarction		18 (35%)	16 (31%)	6 (12%)	–	9 (18%)	–	2 (4%)	51 (100%)
Atherothrombotic brain infarction		1 (6%)	14 (82%)	–	1 (6%)	1 (6%)	–	–	17 (100%)
Cardioembolic stroke		–	–	16 (94%)	1 (6%)	–	–	–	17 (100%)
Undetermined subtype of BI (UND-BI)		–	–	–	1 (50%)	–	–	1 (50%)	2 (100%)
Brain haemorrhage	5	3 (25%)	1 (8%)	1 (8%)	–	7 (58%)	–	–	12 (100%)
Subarachnoid haemorrhage	2	1 (11%)	1 (11%)	–	–	1 (11%)	6 (67%)	–	9 (100%)
Undetermined type of stroke	–	–	–	–	–	–	–	–	0 (0%)

Percentages are the proportions of types or subtypes of recurrent stroke calculated using the numbers of total recurrent stroke as the denominators.
AT, atherothrombotic brain infarction; BH, brain haemorrhage; BI, brain infarction; CE, cardioembolic stroke; LA, lacunar infarction; SAH, subarachnoid haemorrhage; UND, undetermined.

Hypertension is a major risk factor for both lacunar infarction and brain haemorrhage, and lesions of all lacunar infarcts and most brain haemorrhages in our patients were located in brain areas that have the common feature of penetrating arteries, such as the basal ganglia, thalamus, and pons. These similarities would support the overlap between lacunar infarction and brain haemorrhage in recurrent stroke types.

Study limitations

There are several potential limitations to the findings in our study. First, we enrolled stroke cases that developed among an inception cohort during 32 years of follow up. The prevalence of cardiovascular risk factors and the risk of stroke recurrence may have changed widely during this long term observation period.[25] Secular trends in stroke recurrence should be examined, and we will do so in another study. Second, the study did not consider the effects of cardiovascular risk factors or those of medical or surgical treatment. Thus our estimates for the risk of stroke recurrence are probably quite conservative. Third, brain imaging was available in only 37% of the index stroke cases. However, we collected available clinical information on both index and recurrent strokes in minute detail and carried out necropsies on 84% of deceased stroke patients. We believe that our exhaustive and careful evaluation of the clinical information, as well as the high rate of necropsy, improved the quality and validity of the diagnosis as well as the stroke classification in our study.

Conclusions

Our findings show higher recurrence rates of stroke in a Japanese community than in Western populations. The divergent patterns of stroke recurrence after index lacunar infarction or brain haemorrhage are of interest and importance for the prevention of recurrent stroke, because the Japanese are characterised by high morbidity of lacunar infarction and brain haemorrhage. The consistent increase in cumulative recurrence rates during the long observation period and the higher recurrence rates after index brain infarction among older patients are both important for medical care. We believe that these findings will contribute to a better understanding of stroke recurrence in the Japanese, who are considered to be at greater risk of stroke than other populations.

Authors' affiliations

J Hata, Y Tanizaki, Y Kiyohara, I Kato, M Kubo, K Tanaka, K Okubo, H Nakamura, Y Oishi, S Ibayashi, M Iida, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Competing interests: none declared

REFERENCES

1 **Sacco RL**, Benjamin EJ, Broderick JP, *et al.* Risk factors. *Stroke* 1997;**28**:1507–17.
2 **Kiyohara Y**, Kubo M, Kato I, *et al.* Ten-year prognosis of stroke and risk factors for death in a Japanese community: the Hisayama Study. *Stroke* 2003;**34**:2343–7.
3 **Hankey GJ**, Jamrozik K, Broadhurst RJ, *et al.* Long-term risk of first recurrent stroke in the Perth Community Stroke Study. *Stroke* 1998;**29**:2491–500.
4 **Hillen T**, Coshall C, Tilling K, *et al.* Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London Stroke Register. *Stroke* 2003;**34**:1457–63.
5 **Burn J**, Dennis M, Bamford J, *et al.* Long-term risk of recurrent stroke after a first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke* 1994;**25**:333–7.
6 **Bamford J**, Sanderchok P, Dennis M, *et al.* Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet* 1991;**337**:1521–6.
7 **Petty GW**, Brown RD, Whisnant JP, *et al.* Ischemic stroke subtypes: a population-based study of functional outcome, survival, and recurrence. *Stroke* 2000;**31**:1062–8.
8 **Kolominsky-Rabas PL**, Weber M, Gefeller O, *et al.* Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke* 2001;**32**:2735–40.
9 **Sacco RL**, Shi T, Zamanillo MC, *et al.* Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. *Neurology* 1994;**44**:626–34.
10 **Hier DB**, Foulkes MA, Swiontoniowski M, *et al.* Stroke recurrence within 2 years after ischemic infarction. *Stroke* 1991;**22**:155–61.
11 **Petty GW**, Brown RD, Whisnant JP, *et al.* Survival and recurrence after first cerebral infarction: a population-based study in Rochester, Minnesota, 1975 through 1989. *Neurology* 1998;**50**:208–16.
12 **Nadeau SE**, Jordan JE, Mishra SK, *et al.* Stroke rates in patients with lacunar and large vessel cerebral infarctions. *J Neurol Sci* 1993;**114**:128–37.
13 **Yamamoto H**, Bogousslavsky J. Mechanisms of second and further strokes. *J Neurol Neurosurg Psychiatry* 1998;**64**:771–6.
14 **Sacco RL**, Wolf PA, Kannel WB, *et al.* Survival and recurrence following stroke: the Framingham Study. *Stroke* 1982;**13**:290–5.
15 **Special report from the National Institute of Neurological Disorders**, Stroke: Classification of Cerebrovascular Diseases III. *Stroke* 1990;**21**:637–76.
16 **Adams HP**, Bendixen BH, Kappelle LJ, *et al.* Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. *Stroke* 1993;**24**:35–41.
17 **Cerebral Embolism Task Force**. Cardiogenic brain embolism. *Arch Neurol* 1986;**43**:71–84.
18 **Katsuki S**. Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* 1966;**21**:64–89.
19 **Tanizaki Y**, Kiyohara Y, Kato I, *et al.* Incidence and risk factors for subtypes of cerebral infarction in a general population: the Hisayama Study. *Stroke* 2000;**31**:2616–22.
20 **Cerebral Embolism Task Force**. Cardiogenic brain embolism: the second report of the Cerebral Embolism Task Force. *Arch Neurol* 1989;**46**:727–43.
21 **Yasaka M**, Yamaguchi T, Oita J, *et al.* Clinical features of recurrent embolization in acute cardioembolic stroke. *Stroke* 1993;**24**:1681–5.
22 **Fisher CM**. Lacunar strokes and infarcts: a review. *Neurology* 1982;**32**:871–6.
23 **Caplan LR**. Intracranial branch atheromatous disease: a neglected, understudied, and underused concept. *Neurology* 1989;**39**:1246–50.
24 **Horowitz DR**, Tuhrim S, Weinberger JM, *et al.* Mechanisms in lacunar infarction. *Stroke* 1992;**23**:325–7.
25 **Kubo M**, Kiyohara Y, Kato I, *et al.* Trends in the incidence, mortality, and survival rate of cardiovascular disease in a Japanese community: the Hisayama Study. *Stroke* 2003;**34**:2349–54.

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

The Hisayama Study

YASUFUMI DOI, MD
YUTAKA KIYOHARA, MD
MICHIAKI KUBO, MD
YUMIHIRO TANIZAKI, MD
KEN OKUBO, MD
TOSHIHARU NINOMIYA, MD
MASANORI IWASE, MD
MITSUO IIDA, MD

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,

From the Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.
Address correspondence and reprint requests to Yasufumi Doi, MD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. E-mail: doi@intmed2.med.kyushu-u.ac.jp.
Received for publication 13 December 2004 and accepted in revised form 24 January 2005.
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.

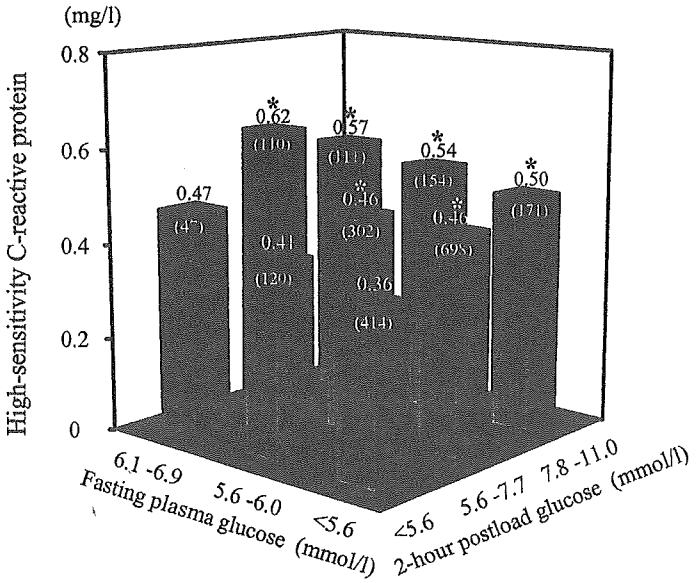

Figure 1—*High-sensitivity C-reactive protein (CRP) levels according to fasting plasma glucose and 2-h postload glucose levels. Multivariate adjustments were made for age, sex, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, hypertension, smoking habits, and alcohol intake. Parentheses 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

Miho Miyazaki,[1] *Yutaka Kiyohara,*[2] *Ayako Yoshida,*[1] *Mitsuo Iida,*[2] *Yoshiaki Nose,*[3] *and Tatsuro Ishibashi*[1]

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

From the Departments of [1]Ophthalmology, [2]Medicine and Clinical Science, and [3]Medical Information Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

Submitted for publication August 2, 2004; revised December 16, 2004, and January 31, 2005; accepted February 8, 2005.

Disclosure: **M. Miyazaki**, None; **Y. Kiyohara**, None; **A. Yoshida**, None; **M. Iida**, None; **Y. Nose**, None; **T. Ishibashi**, None

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Corresponding author: Miho Miyazaki, Department of Ophthalmology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan; miho-m@info.med.kyushu-u.ac.jp.

(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 ($\times 10^3$/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)