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

The Hisayama Study

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

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

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

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

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

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

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

RESEARCH DESIGN AND METHODS

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

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Abbreviations: FPG, fasting plasma glucose.

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

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

Follow-up survey

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

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

Laboratory testing and risk factor measurement

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

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

Statistical analysis

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

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

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

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

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

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

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

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

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

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

In this study, the age-adjusted inci-

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

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

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

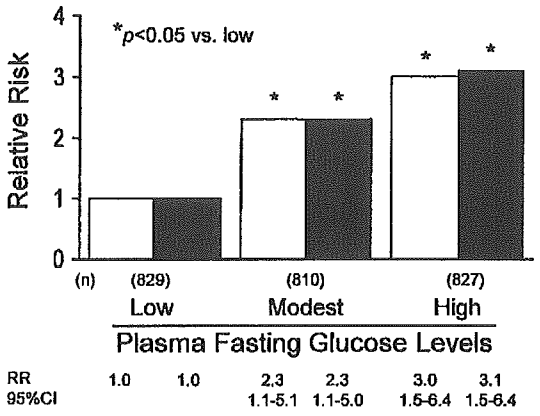

Figure 1—*Age- and sex-adjusted (□) and multivariate-adjusted (■) RR of gastric cancer of the modest-FPG (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group. In the multivariate analysis, the RR is adjusted for age, sex, BMI, serum cholesterol,* H.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

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

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

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

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

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

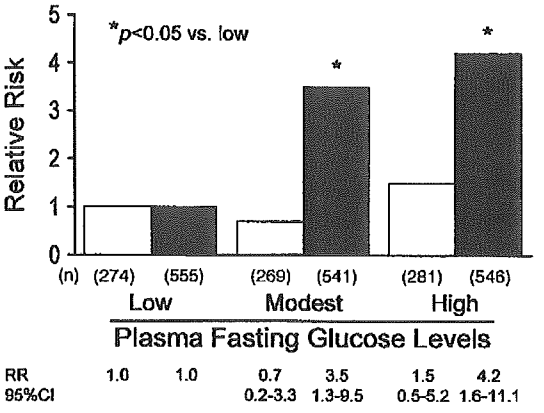

Figure 2—*Age- and sex-adjusted RR of gastric cancer of the modest (5.3–5.8 mmol/l) and high-FPG (>5.8 mmol/l) groups compared with that of the low-FPG (<5.3 mmol/l) group under stratification by* H. pylori *status.* □, H. pylori *seronegative;* ■, H. pylori *seropositive.*

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

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

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

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

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

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

The Hisayama Study

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

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

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

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

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

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

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

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

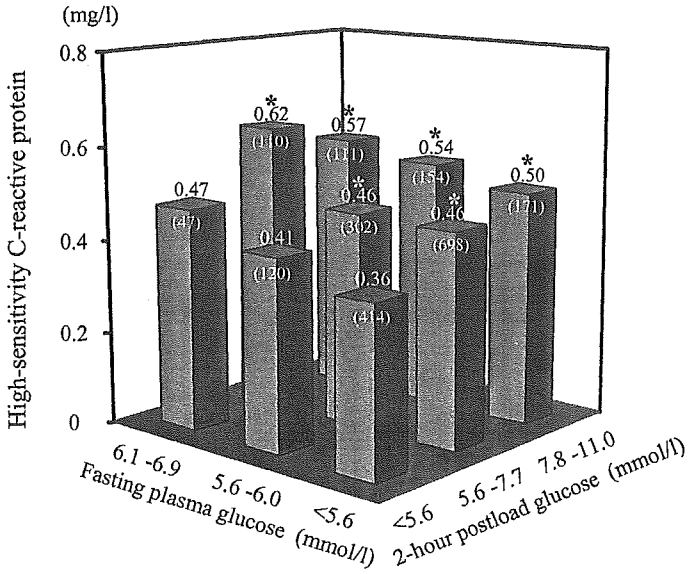

Figure 1—*High-sensitivity C-reactive protein (CRP) levels according to fasting plasma glucose and 2-h postload glucose levels. Multivariate adjustments were made for age, sex, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, hypertension, smoking habits, and alcohol intake. Parentheses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

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Elevated C-Reactive Protein Is a Predictor of the Development of Diabetes in a General Japanese Population

The Hisayama Study

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OBJECTIVE — We examined the association between high-sensitivity C-reactive protein (CRP) levels and the development of diabetes in a general Japanese population.

RESEARCH DESIGN AND METHODS — A total of 1,759 Japanese subjects, aged 40–79 years and without diabetes (according to American Diabetes Association fasting criteria), were stratified into three groups according to CRP tertiles by sex and followed up prospectively for a mean of 9.0 years.

RESULTS — During the follow-up, 131 subjects (67 men and 64 women) developed diabetes. In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly as the tertiles of CRP levels increased. In multivariate analyses, the risk of developing diabetes was significantly higher in the highest CRP tertile than in the lowest after adjustment for a number of confounding factors (odds ratio 2.63 [95% CI 1.23–5.65] for men and 2.25 [1.01–5.01] for women). In stratified analyses, this CRP-diabetes association was stronger in subjects without obesity or other risk factors related to insulin resistance and in nondrinking subjects.

CONCLUSIONS — Our findings suggest that elevated CRP concentration is a significant predictor of diabetes in the general Japanese population, independent of obesity and insulin resistance.

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In some cohort and nested case-control studies in Western countries, an elevated C-reactive protein (CRP) level has been an independent predictor of diabetes (1–10). Recent cross-sectional studies have also demonstrated clear associations of elevated serum CRP levels with obesity and insulin resistance (11–13). These findings suggest that the inflammatory state illustrated by elevated CRP concentrations is associated with hyperglycemia and diabetes through obesity or increased insulin resistance. However, epidemiological findings concerning this issue are still controversial; several studies have reported a significant positive association between elevation in CRP levels and the future risk of diabetes even after adjustment for BMI (1,2,4,7,9,10), whereas in other studies (3,6) this association disappeared after adjustment for BMI.

Japanese are characterized by low BMI levels and low CRP concentrations in blood compared with Westerners (14). Moreover, there have been no reports on the relationship between CRP levels and the development of diabetes among general populations in Japan. The aim of the present study is to examine the effects of serum CRP levels on the development of diabetes in a prospective study of a defined Japanese population, taking into account comprehensive risk factors.

RESEARCH DESIGN AND METHODS

Study population and follow-up survey

In 1988, a screening survey for the present study was performed in the Town of Hisayama in Japan. A total of 2,587 residents aged 40–79 years (80.2% of the total population of this age-group) participated in the baseline survey. The diabetes classification was based on the fasting criteria of the American Diabetes Association (15), i.e., subjects with fasting plasma glucose levels ≥7.0 mmol/l or those who were taking diabetes medications were considered diabetic.

After the exclusion of 80 subjects who had already eaten breakfast before the examination, 233 subjects with diabetes, and 67 subjects whose CRP concentrations could not be measured due to insufficient quantities of stored sera, the remaining 2,207 subjects (926 men and 1,281 women) were enrolled in the baseline examination. Among those, 1,759 subjects (694 men and 1,065 women) underwent follow-up examinations in 1993–1998 (follow-up rate 79.7%). We considered a subject to have developed diabetes when he/she met the above-mentioned baseline criteria. During this period, 131 subjects (67 men and 64 women) developed diabetes.

Laboratory measurements

Plasma glucose levels were determined by a glucose-oxidase method, and serum insulin was measured by radioimmunoassay. HbA_{1c} levels were measured by high-pressure liquid chromatography. Total cholesterol, HDL cholesterol, and triglycerides were all determined enzymatically. Serum specimens collected at the time of CRP measurement were stored at −20°C until used in 2002. High-sensitivity CRP

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Abbreviations: CRP, C-reactive protein.
A table elsewhere in this issue shows conventional and Systeme International (SI) units and conversion factors for many substances.

concentrations were determined using a modification of the Behring latex-enhanced CRP assay. Sitting blood pressure was obtained three times and the average values used in the analyses. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or current treatment with antihypertensive agents. BMI (kilograms per meters squared) was used as an indicator of obesity.

Diabetes in first- or second-degree relatives indicated a family history of diabetes. Those subjects engaging in sports at least three times a week during their leisure time comprised a regular exercise group. Information on smoking habits and alcohol intake was used to classify subjects as having current habits or not.

Table 1—*Characteristics of subjects by sex*

	Men	Women
n	694	1,065
Age (years)	58 ± 10	57 ± 10
High-sensitivity CRP (mg/l)	0.49 (0.07–7.14)	0.36 (0.06–3.22)
Fasting plasma glucose (mmol/l)	5.6 ± 0.5	5.5 ± 0.5
HbA_{1c} (%)	5.5 ± 0.5	5.4 ± 0.5
Family history of diabetes (%)	9.3	7.3
Fasting insulin (pmol/l)	30.0 (18.0–72.0)	36.0 (18.0–72.0)
BMI (kg/m^2)	22.9 ± 2.9	23.0 ± 3.1
Total cholesterol (mmol/l)	5.10 ± 1.04	5.57 ± 1.05
HDL cholesterol (mmol/l)	1.26 ± 0.30	1.35 ± 0.29
Triglycerides (mmol/l)	1.25 (0.58–3.49)	1.02 (0.49–2.33)
Systolic blood pressure (mmHg)	131 ± 19	130 ± 20
Diastolic blood pressure (mmHg)	80 ± 11	75 ± 11
Hypertension (%)	41.5	32.7
Current drinking (%)	61.0	8.5
Current smoking (%)	47.6	5.4
Regular exercise (%)	16.1	4.9

Data are means ± SD or medians (95% CI) unless otherwise indicated.

Statistical analysis

Because the distributions of CRP, fasting insulin, and triglycerides were skewed, these variables were natural log transformed for statistical analyses. To analyze CRP levels as categorical variables, these levels were divided into tertiles by sex (0.05–0.28, 0.29–0.77, and 0.78–13.5 mg/l for men and 0.05–0.24, 0.25–0.57, and 0.58–5.78 mg/l for women). The age-adjusted cumulative incidence of diabetes was calculated by the direct method and compared by the Mantel-Haenszel χ^2 test using 10-year age-groupings. Age- and multivariate-adjusted odds ratios (ORs) and 95% CIs were calculated by logistic regression analysis. $P < 0.05$ was considered statistically significant in all analyses.

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

RESULTS — The clinical characteristics of the subjects by sex are shown in Table 1. The mean age was 58 years for men and 57 years for women.

In both sexes, the age-adjusted cumulative incidence of diabetes increased significantly with elevating tertiles of baseline serum CRP concentrations. The incidences in the 3rd tertile for both sexes and in the 2nd tertile for men were significantly higher than in the 1st tertile (Fig. 1). As shown in Table 2, the risk of future diabetes in either sex was more than threefold higher in the 3rd tertile than in the 1st tertile after adjustment for age. These associations remained substantially unchanged even after adjustment for the other confounding factors, including age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity (adjusted OR 2.63 [95% CI 1.23–5.65], $P = 0.014$, for men and 2.25 [1.01–5.01], $P = 0.049$, for women).

We next estimated the age- and sex-adjusted ORs and 95% CIs for the development of diabetes by an increment of 1 log CRP in men and women together according to the other risk factor levels (Table 3). Analyses were performed by dividing the subjects into three groups according to tertiles of BMI, triglycerides, and HDL cholesterol levels or into two

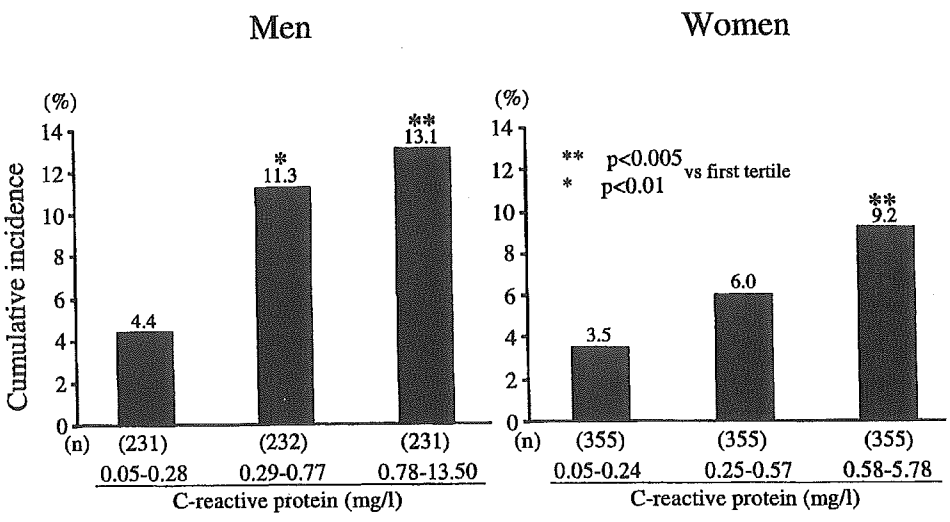

Figure 1—*Age-adjusted cumulative incidence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex.*

Table 2—*Age- or multivariate-adjusted ORs and 95% CIs for occurrence of diabetes according to tertiles of serum high-sensitivity CRP levels by sex*

	High-sensitivity CRP level (mg/l)							
	Men				Women			
	0.05–0.28	0.29–0.77	0.78–13.50	*P* for trend	0.05–0.24	0.25–0.57	0.58–5.78	*P* for trend
Population at risk (*n*)	231	232	231		355	355	355	
Cases of diabetes (*n*)	11	26	30		10	21	33	
Age-adjusted OR (95% CI)	1 (referent)	2.67 (1.28–5.56)	3.23 (1.57–6.70)	0.002	1 (referent)	2.12 (0.98–4.58)	3.35 (1.60–7.03)	0.001
Multivariate-adjusted OR (95% CI)	1 (referent)	1.96 (0.92–4.19)	2.63 (1.23–5.65)	0.014	1 (referent)	1.76 (0.80–3.87)	2.25 (1.01–5.01)	0.049

Multivariate adjustment was made for age, family history of diabetes, fasting insulin, BMI, total cholesterol, HDL cholesterol, triglycerides, systolic blood pressure, current drinking, current smoking, and physical activity.

groups by hypertension status, current drinking, and current smoking. Significant positive associations between CRP levels and incident diabetes were observed among subjects in the 1st tertile of BMI, among subjects in the 1st and 2nd tertiles of triglycerides, among subjects of the 2nd and 3rd tertiles of HDL cholesterol, and among subjects without hypertension or current drinking. Significant associations were also observed in both smokers and nonsmokers. However, clear CRP-diabetes associations were not seen in the other categories of any risk factors.

CONCLUSIONS— We demonstrated in a prospective study of a general Japanese population that elevated CRP level is an independent predictor of diabetes for both sexes even after adjustment for comprehensive risk factors. In stratified analyses, the CRP-diabetes association was stronger in subjects without risk factors related to insulin resistance, such as obesity, dyslipidemia, and hypertension, and among nondrinkers, whereas the presence of a current smoking habit did not affect this association.

To our knowledge, this is the first report to indicate that the low-grade inflammatory state illustrated by increased CRP is an independent risk factor for developing diabetes in a general Japanese population. Similar findings were observed in a Japanese-American population (13) as well as in some other Western populations (5–12,14). Since Japanese Americans have a Western lifestyle, their findings cannot be generalized to Japanese living in Japan. Our subjects were thinner than those in previous reports (1–10). Our findings suggest that the subclinical inflammatory process has an important role in the development of diabetes in relatively lean Asian populations, as it does in Western populations.

Recent cross-sectional epidemiological data have demonstrated that elevated serum CRP levels are associated with obesity, insulin resistance, and glucose intolerance (11–13). These findings suggest that the inflammatory state affects glucose levels in blood and increases the risk of diabetes via obesity or insulin resistance. However, our study showed that the association between CRP levels and the development of diabetes is independent of serum insulin levels as well as BMI. These findings are in accord with those of several other cohort studies (1,9). Additionally, our stratified analyses showed that the CRP-diabetes association was stronger particularly in individuals with low levels of risk factors related to insulin resistance. Therefore, a low-grade inflammatory state can be considered a risk factor for diabetes independent of obesity and insulin resistance, and unknown mediators are also thought to be involved in the development of diabetes.

In our subjects, the influence of CRP on the incidence of diabetes was stronger in nondrinkers than in drinkers. Some studies have shown that moderate alcohol

Table 3—*Age- and sex-adjusted ORs and 95% CIs for occurrence of diabetes by an increment of 1 log high-sensitivity CRP in all subjects according to risk-factor levels*

Risk factor	Population at risk (*n*)	Cases of diabetes (*n*)	Age- and sex-adjusted OR (95% CI)	*P*
BMI (kg/m^2)				
≤21.5	586	29	1.36 (1.05–1.75)	0.017
21.6–24.2	587	35	1.20 (0.92–1.57)	NS
≥24.3	586	67	1.25 (0.99–1.59)	NS
Triglycerides (mmol/l)				
≤0.88	587	30	1.30 (1.01–1.67)	0.042
0.89–1.34	582	29	1.50 (1.12–2.01)	0.007
≥1.35	590	72	1.16 (0.94–1.43)	NS
HDL cholesterol (mmol/l)				
≤1.14	572	49	1.04 (0.82–1.31)	NS
1.15–1.40	583	44	1.43 (1.13–1.81)	0.003
≥1.41	604	38	1.57 (1.20–2.07)	0.001
Hypertension				
Without	1,123	54	1.45 (1.18–1.77)	0.0003
With	636	77	1.16 (0.95–1.41)	NS
Current drinking				
Without	1,246	77	1.43 (1.20–1.71)	0.0001
With	513	54	1.14 (0.92–1.42)	NS
Current smoking				
Without	1,372	95	1.29 (1.09–1.53)	0.003
With	387	36	1.34 (1.04–1.72)	0.022

consumption is associated with lower CRP concentrations (16,17). Additionally, recent cohort studies have revealed that moderate alcohol consumption reduced the risk of future type 2 diabetes (18,19). Therefore, the intake of alcohol may attenuate the influence of CRP on the development of diabetes.

A recent cohort study has reported a significant association between inflammation and future diabetes among nonsmokers but not among smokers (8). In our subjects, however, an association between elevated CRP levels and incident diabetes was observed in both nonsmokers and smokers. This suggests that the CRP-diabetes association is independent of current smoking.

Several limitations of our study should be discussed. The primary limitation is that a diagnosis of diabetes was not based on a 75-g oral glucose tolerance test, but on a single reading of fasting glucose level, as was the case in other epidemiological studies (2,8,9). Subjects with diabetes having normal fasting glucose levels were misdiagnosed in our study. Additionally, some of the participants who were classified as having worsening fasting glucose status may not have been so categorized after repeated testing. These misclassifications should weaken the association found in this study. Therefore, the true association may be stronger than that shown in our findings. A secondary limitation is that CRP concentrations were measured in serum conserved for a long period at −20°C. However, the stability of CRP concentrations in serum preserved at this temperature for an average of 12 years was confirmed in the Reykjavik Study (20). The last limitation is that our study lacked information on drug use, which could affect serum CRP levels. It is known that several medications can alter CRP levels, including statins, ACE inhibitors, fibrates, niacin, thiazolidinedione, and estrogen/progestogen hormone (21). However, these medications were rarely used in our country in 1988. This suggests that such a bias does not invalidate the present findings.

In conclusion, we showed that subclinical elevation in CRP concentrations is an independent predictor of diabetes in a general Japanese population. CRP was an effective predictor of diabetes in individuals with the lowest BMI as well as in individuals without other risk factors related to insulin resistance. These findings add to the notion that low-grade inflammation is an important factor in the pathogenesis of type 2 diabetes. Further study is necessary to clarify the role of inflammation in the cascade to the development of diabetes.

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

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

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

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

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

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

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

Methods

Study Population

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

Ophthalmic Examination and Definition of Age-Related Maculopathy

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

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

Data Collection

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

Statistical Methods

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

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

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

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

Ethical Considerations

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

RESULTS

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

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

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

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

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

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

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

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

DISCUSSION

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

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

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

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

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

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

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

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

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

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

* $P < 0.05$

† OR; odds ratio

‡ CI; confidence interval

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

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

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

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ORIGINAL ARTICLE

The Prevalence of Pseudoexfoliation Syndrome in a Japanese Population: The Hisayama Study

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Purpose: To examine the prevalence and systemic associations of pseudoexfoliation syndrome (PXS) in a Japanese population.

Methods: In 1998, a cross-sectional population-based survey was conducted among residents of Hisayama. Of a total of 3054 residents living in Hisayama, Japan, aged 50 years or older, 1844 consented to participate in the study. Each participant underwent a comprehensive examination that included an ophthalmic examination. The presence of any pseudoexfoliation material on the iris or lens capsule was determined by slit-lamp examination. The participants were classified as having pseudoexfoliation syndrome if any pseudoexfoliation material was present in either eye. Using these cross-sectional data, logistic regression analyses were performed to determine the systemic associations of pseudoexfoliation syndrome. The following eight possible correlates were considered: age, sex, hypertension, diabetes, hyperlipidemia, current smoker, alcohol intake, and body mass index.

Results: Among the subjects, 50 (3.4%) had pseudoexfoliation syndrome. The prevalence of pseudoexfoliation syndrome increased significantly with age. Multiple logistic regression analysis showed that age and hypertension were significantly associated with pseudoexfoliation syndrome.

Conclusion: The prevalence of pseudoexfoliation syndrome in a Japanese population was 3.4%, and increased with age. This study suggests that hypertension strongly correlates with pseudoexfoliation syndrome in our population-based sample of Japanese subjects aged 50 years or older.

Key Words: Hypertension, Japanese population, population-based study, prevalence, pseudoexfoliation syndrome

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INTRODUCTION

Pseudoexfoliation syndrome (PXS) is an age-related disease characterized by the production and progressive accumulation of a fibrillar extracellular material in many ocular tissues.[1] Its ocular manifestations involve all of the structures of the anterior segment, as well as conjunctiva and orbital structures. Glaucoma occurs more commonly in eyes with PXS than in those without it.[2] Based on the recent electron microscopic identification of accumulations of pseudoexfoliation fibers in orbital tissues,[3] skin specimens,[4] and visceral organs,[5,6] PXS has recently been recognized as a generalized or systemic disorder of the extracellular matrix. Systemic associations reported include angina, hypertension, myocardial infarction, stroke, and abdominal aortic aneurysm.[7,8] However, no clear-cut association of PXS with a systemic disease has yet been shown.

The prevalence of PXS in various populations was reported; however, to our knowledge, no population-based studies have examined the systemic associations of PXS in Japan. Therefore, the primary aim of our study is to investigate the systemic associations of PXS in a representative sample of Japanese aged 50 years and older.

PATIENTS AND METHODS

Study Population

The Hisayama study is an ongoing prospective cohort study on cardiovascular disease and its risk factors in a community of Hisayama Town adjoining Fukuoka City, a metropolitan area in southern Japan. The enrollment criteria, characteristics of the study population, and overall design of this study have been previously described in detail.[9,10] As a part of follow-up survey, we performed a cross-sectional examination, including an eye examination, of Hisayama residents aged 50 years or older in 1998. Of a total 3054 residents in that age group, 1844 subjects (60.4%) consented to participate in the study. After excluding 349 subjects who underwent the examination at home, and 31 in whom bilateral cataract surgery had been performed, a total of 1464 individuals (588 men and 876 women) were enrolled in the present study.

Ophthalmic Examination

The methods used in the ophthalmic examination have been described in detail previously.[11] Briefly, each participant underwent ophthalmic examinations, including clinical slit-lamp examination after pupil dilation. The presence of any

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exfoliation material on the iris or lens capsule was determined by slit-lamp examination. Participants were classified as having PXS if any exfoliation material was present in either eye, and analyses were based on individuals, not per eye.

Data Collection

Blood pressure was measured 3 times after resting for at least 5 minutes in the sitting position. The average of the 3 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 an antecubital vein after an overnight fast for the determination of plasma glucose and HbA_{1c} levels. After the fasting blood specimen had been taken, the OGTT was performed with a 75-g glucose equivalent carbohydrate load (Trelan G; Shimizu Pharmaceutical, Shimizu, Japan). Diabetes was defined as a fasting plasma glucose level ≥7.0 mmol/L, or a 2-hour post-loading glucose level ≥11.1 mmol/L, or a medical history of diabetes. The total cholesterol and serum triglyceride levels were determined enzymatically using an autoanalyzer (TBA-80S; Toshiba Inc., Tokyo, Japan), and hyperlipidemia was defined as a total cholesterol level ≥5.7 mmol/L, serum triglyceride level ≥1.7 mmol/L, or current use of antihyperlipidemic medication. Information on smoking habits and alcohol intake was obtained using a standard questionnaire, and these factors were classified into either current habitual use or non-use. 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 height in meters squared.

Statistical Methods

We considered the following 8 possible correlates of PXS: age, sex, hypertension, diabetes, hyperlipidemia, current smoker, alcohol intake, and BMI. Age and BMI were treated as continuous variables and the others as categorical variables. Each categorical variable was coded as either 1 or 0 depending upon 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 of each potential risk factor by using a stepwise logistic regression analysis. Only variables with a P value of less than 0.05 were entered into or allowed to remain in the stepwise multivariate regression analysis. The SAS computer package (SAS Institute, Cary, NC) was used to perform all the statistical analyses. A two-sided P value less than 0.05 was considered statistically significant.

Ethical Consideration

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

RESULTS

Among the study participants, 50 (3.4%) were found to have exfoliation materials. Table 1 shows the age-specific prevalence of PXS by sex. The overall prevalence was 3.5% in women and 3.2% in men, but the difference was not significant. PXS significantly increased with advancing age in all participants and in women (Cochran-Armitage Trend Test; $P = 0.001$). T1

We compared the mean values or frequencies of possible correlates in subjects with and without PXS (Table 2). The subjects with PXS were significantly older than those without PXS ($P < 0.01$). Hypertension was significantly more frequent in those with PXS ($P < 0.05$). T2

The results of age-adjusted and multivariate-adjusted logistic regression analyses of correlates of PXS are shown in Table 3. After adjusting for age, hypertension was significantly associated with PXS. Also, the multivariate regression analysis showed that age and hypertension were significantly associated with PXS. The results show that hypertension is 1.41 times more likely in patients with PXS versus patients without PXS. T3

DISCUSSION

The current study was performed as a part of a prospective cohort study in a representative Japanese population, the Hisayama study, which has been carried out since 1961. To our knowledge, this is the first study to investigate the systemic associations of PXS in Japan, using a population-based sample. The results show that the prevalence of PXS was 3.4%, and that age and hypertension were significantly associated with PXS.

The reported prevalence of PEX in different populations shows extensive variations—Eskimo (0%),[12] China (0.4%),[13] Australia (0.98),[14] America (1.8%),[15] India (3.8%),[16] England (4%),[17] Germany (4.7%),[17] Norway (6.3%),[12] Finland (22%),[12] and Iceland (29%).[12] The overall prevalence of 3.4% in the Hisayama Study is similar to that in Western Europe and to that in India. These could reflect true variations arising from racial, genetic, or geographical differences. However, some of the

TABLE 1. Age-specific Prevalence of Pseudoexfoliation Syndrome by Sex, the Hisayama Study, 1998

	Men		Women		All	
	Number of Subjects	Pseudoexfoliation N (%)	Number of Subjects	Pseudoexfoliation N (%)	Number of Subjects	Pseudoexfoliation N (%)
50–59	154	0 (0.0)	282	2 (0.7)	436	2 (0.5)
60–69	226	7 (3.1)	331	13 (3.9)	557	20 (3.6)
70–79	176	12 (6.8)	211	10 (4.7)	387	22 (5.7)
80+	32	0 (0.0)	52	6 (11.5)	84	6 (7.1)
Total	588	19 (3.2)	876	31 (3.5)	1464	50 (3.4)

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TABLE 2. Mean Values or Frequencies of Possible Correlates of Pseudoexfoliation Syndrome, the Hisayama Study, 1998

Variables	Non-Pseudoexfoliation (n = 1414)	Pseudoexfoliation (n = 50)
Age (year)	65 ± 9	71 ± 7*
Sex (men/women)	569/845	19/31
Hypertension (%)	42.0	50.2
Diabetes (%)	13.0	8.7
Hyperlipidemia (%)	52.7	58.0
Current smoker (%)	16.5	18.0
Alcohol intake (%)	35.6	38.0
Body mass index (kg/m^2)	23.1 ± 3.2	22.6 ± 3.3

Values are expressed as the mean ± SD or percent.
*$P < 0.05$, pseudoexfoliation vs. non-pseudoexfoliation.

variability could be explained by differences in techniques of assessment and age distributions in the sampled populations.

In our Japanese subjects, the prevalence of PXS significantly increased with advancing age. It is well known that the prevalence of PXS increases with age. The findings are similar to those of other studies.[1,7,16] There was no significant difference in sex distribution in our study, which is also in accordance with other studies,[16] although some studies have reported a female preponderance.[15]

We found a strong relationship between PXS and hypertension. In the Blue Mountains Eye Study, PXS was found to correlate positively with a history of hypertension, angina, myocardial infarction, or stroke, suggestive of vascular effects of the disease.[7] In a small pilot study, PXS was significantly associated with aneurysms of the abdominal aorta.[18] The exact etiology and pathogenesis are unclear, but recent work shows that pseudoexfoliation is a form of elastosis.[19] Elastin is a major component of the extracellular matrix of arterioles. These findings suggest that abnormal elastic fiber and elastin synthesis greatly affected vessel walls, thus resulted in an increased risk of vascular diseases.

Several factors limit the interpretation of our results. First, our results might be biased by the low participation rate.

TABLE 3. Crude and Age-Adjusted Odds Ratios of Correlates of Pseudoexfoliation, the Hisayama Study, 1998

	Age-Adjusted		Multivariate-Adjusted*	
Variables	OR§	95% CI§	OR¶	95% CI§
Age†			1.07^	1.04–1.11
Sex (women vs. men)	1.15	0.64–2.07		
Hypertension	1.92^	1.07–3.46	1.92^	1.07–3.46
Diabetes	0.57	0.20–1.62		
Hyperlipidemia	1.36	0.76–2.43		
Current smoker	1.20	0.57–2.52		
Alcohol intake	1.27	0.71–2.30		
Body mass index‡	0.98	0.90–1.08		

*Adjusted for age, sex, hypertension, diabetes, hyperlipidemia, current smoker, alcohol intake, and body mass index, using the stepwise method; †OR for an increase of 1 year; ‡OR for an increase of 1 kg/m^2; §OR, odds ratio; ¶CI, confidence interval; ^$P < 0.05$.

To ascertain the possibility of this bias, we compared the mean values of age and the proportion of either gender between the participants in ophthalmic examination and the nonparticipants. However, no significant differences in these parameters were observed between these groups (data not shown), suggesting that this limitation does not largely invalidate the findings of the present study. Second, because of the cross-sectional design of this study, it is still unclear how PXS is related to hypertension. Additional prospective studies will help clarify the causal relationships between hypertension and PXS.

In conclusion, we found a 3.4% prevalence of PXS in a representative sample of Japanese aged 50 years and older. Furthermore, our population-based study suggests that age and hypertension are correlates of PXS in Japanese.

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