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)

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

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Key words: gastric cancer, incidence, mortality, survival, trend.

Abstract

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

Introduction

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

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

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

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Subjects and methods

Study population

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

Follow-up survey

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

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

Risk factors

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

Statistical analysis

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

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

Results

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

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

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

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

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

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

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

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

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

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

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

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

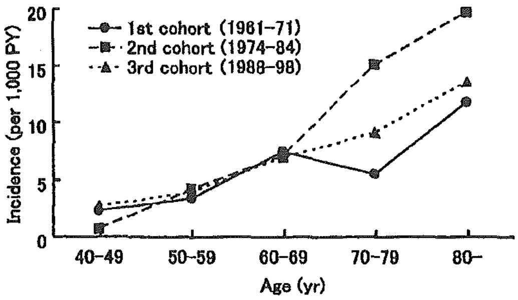

Fig. 1. The age-specific incidence of gastric cancer for men during ten-year follow-up of three Hisayama cohorts.

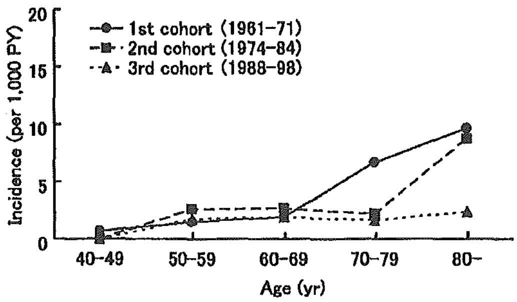

Fig. 2. The age-specific incidence of gastric cancer for women during ten-year follow-up of three Hisayama cohorts.

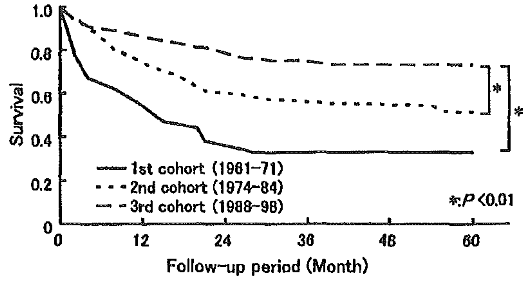

Fig. 3. Age-adjusted five-year survival curves of gastric cancer for men during ten-year follow-up in three Hisayama cohorts.

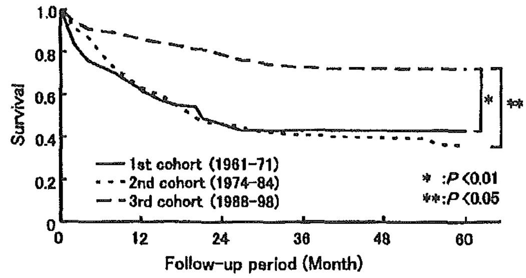

Fig. 4. Age-adjusted five-year survival curves of gastric cancer for women during ten-year follow-up in three Hisayama cohorts.

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Key words: diabetes; epidemiology; glucose tolerance; obesity; periodontal disease; risk factor

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Obesity, which is increasing worldwide, is a major risk factor for adult diseases such as type 2 diabetes, hyperlipemia, hypertension, cholelithiasis, arteriosclerosis, and cardiovascular and cerebrovascular disease (1). Of these disorders, the risk of type 2 diabetes is increased most by obesity, which reduces the glucose tolerance status (1, 2). The results of a Japanese national survey conducted in 1997 revealed that 53% of Japanese with diabetic conditions had previously been obese (body mass index ≥ 26.4) (3). Recent studies have reported that obesity, especially upper-body obesity, is significantly associated with probing pocket depth in the Japanese population (4–6). In the Third National Health and Nutrition Examination Survey (NHANES III), there was a significant association between obesity and periodontal disease in the United States population (7, 8). In addition, type 2 diabetes is a well-documented risk factor for periodontal disease (9–12). Since both type 2 diabetes and periodontal disease take a long time to develop and to manifest in middle-aged people, impaired glucose tolerance as a pre-diabetic condition, caused by obesity, may be a true risk factor for periodontal disease. This implies that obesity and impaired glucose condition are confounding factors associated with periodontal disease. However, no increased risk of periodontal disease with impaired glucose tolerance as a pre-diabetic condition has been reported. A fasting 75-g oral glucose tolerance test is used to diagnose diabetes, as it constitutes the definitive method for assessing a patient's glucose tolerance (13). Although previous reports have considered the role of diabetes in the relationship between obesity and periodontal disease, such studies did not use the oral glucose tolerance test to diagnose diabetic condition. The aforementioned studies used glycosylated hemoglobin A1c, the fasting plasma glucose, or a simple questionnaire about the history of diabetes; therefore, their assessment of diabetes was insufficient. The purpose of this study was to clarify the association between obesity and periodontal disease, with a precise assessment of glucose tolerance status using oral glucose tolerance test, in community-dwelling Japanese women.

Material and methods

From July to September 1998, a total of 982 Hisayama residents aged 40–79 years (21.6% of the total population in that age group) underwent a comprehensive health examination that included both a periodontal examination and a fasting 75-g oral glucose tolerance test (14). In this study, we analyzed 584 women with at least 10 teeth (15, 16).

Following the method of NHANES III (17), a periodontal examination was performed on two randomly selected quadrants, one maxillary and one mandibular, by four trained dentists, using a normal dental chair. Mean probing pocket depth and attachment loss were analyzed. The subjects were divided into quintiles with respect to each of the two periodontal measurements: mean pocket depth and mean attachment loss. Oral hygiene status was evaluated using the plaque index (18).

Blood samples were collected from the antecubital vein the morning after an overnight fast and analyzed using previously described methods (14). The World Health Organization criteria for the diagnosis of diabetes were applied (13). These are as follows: normal glucose tolerance (NGT; fasting plasma glucose level < 110 mg/dl and 2-h post-challenge glucose < 140 mg/dl), diabetes (fasting ≥ 126 mg/dl or 2-h post-challenge ≥ 200 mg/dl), and impaired glucose tolerance (other than the above, including impaired fasting glucose).

Trained nurses measured the subjects' weight, height, and waist and hip circumferences. The waist circumference was measured at the level of the umbilicus. All measurements were taken after the subjects exhaled. The hip circumference was measured around the buttocks 4 cm below the anterior superior iliac spine. As a measure of obesity, three indexes were used. Body mass index (the weight in kilograms divided by the square of the height in meters) and waist–hip ratio were calculated and the body fat of the subjects was measured by the bio-impedance method using a Body Fat Analyzer (TBF-202, TANITA Co., Japan). Each subject completed a self-administered questionnaire in advance, which was checked by trained nurses. Smoking history was estimated from the number of cigarettes smoked per day, multiplied by the number of years smoked; 4.3% of the subjects were current smokers and 2.2% of the subjects were former smokers. Social class was defined from the subjects' occupations as follows: (i) managerial position, (ii) office worker, (iii) primary industry, (iv) factory worker, and (v) homemaker or unemployed.

The differences between the mean values were evaluated using Student's *t*-test and the differences in the percentages were evaluated using the chi-squared test. Logistic regression analyses were used to determine the effect of each variable on the highest quintile of each periodontal parameter (≥ 1.9 mm for mean probing depth; ≥ 2.42 mm for mean attachment loss), and the odds ratio (OR) and 95% confidence interval (CI) were calculated. In bivariate analyses, one of the obesity indexes and the oral glucose tolerance test result were analyzed as independent variables. In the multivariate analysis, age, plaque index, smoking history, and social class were added as independent variables, as known risk factors of periodontal disease (9, 10). SPSS version 11.0 (SPSS Japan Inc., Tokyo, Japan) was used for the analyses. The design of the study and procedures for obtaining informed consent were approved by the Ethics Committee of Kyushu University Faculty of Dental Science and the Department of Health and Welfare of Hisayama town.

Results

The characteristics of the subjects were compared between subjects with the highest quintile of each periodontal parameter (≥ 1.9 mm for mean probing depth; ≥ 2.42 mm for mean attachment loss) and subjects with the four lower quintiles (Table 1). The mean body mass index, body fat, waist–hip ratio, and fasting and 2-h plasma glucose, and the proportion of social class categories differed significantly between subjects with deep and shallow pockets. In comparing the subjects with severe and non-severe attachment loss, the mean fasting and 2-h plasma glucose, hemoglobin A1c, and the proportion of social class categories differed significantly (Table 1). There were fewer teeth and the plaque index was higher in the more aggravated periodontal conditions.

Figure 1 shows the proportion of subjects with each quintile of mean probing pocket depth, according to the quartiles of body mass index, body fat, and waist–hip ratio. The proportion of subjects with the highest quintile of mean probing pocket depth increased significantly in a linear fashion with the quartiles of body mass index ($p < 0.0001$), body fat ($p = 0.0003$), and waist–hip ratio ($p = 0.007$). Figure 2

Table 1. Characteristics of subjects in each periodontal condition in Japanese women

Characteristics	Mean PD < 1.9 mm $n = 469$	Mean PD ≥ 1.9 mm $n = 114$	p*	Mean AL < 2.42 mm $n = 467$	Mean AL ≥ 2.42 mm $n = 116$	p*
	Mean (SD)			Mean (SD)		
Age (years)	55.5 (8.9)	56.8 (8.3)	0.14	54.8 (8.6)	59.4 (8.3)	< 0.0001
Number of teeth	25.4 (3.6)	23.5 (4.3)	< 0.0001	25.5 (3.6)	22.8 (4.0)	< 0.0001
Mean PD (mm)	1.4 (0.3)	2.3 (0.4)	< 0.0001	1.4 (0.4)	2.1 (0.5)	< 0.0001
Mean AL (mm)	1.7 (0.5)	2.7 (0.6)	< 0.0001	1.6 (0.5)	2.9 (0.5)	< 0.0001
Plaque index	0.9 (0.5)	1.4 (0.6)	< 0.0001	0.9 (0.5)	1.3 (0.6)	< 0.0001
Body mass index (kg/m^2)	22.9 (3.5)	24.1 (2.9)	0.0004	23.0 (3.5)	23.6 (3.1)	0.09
Body fat (%)	28.0 (6.1)	30.4 (5.7)	0.0002	28.3 (6.1)	29.1 (6.1)	0.26
Waist–hip ratio	0.93 (0.06)	0.94 (0.05)	0.027	0.93 (0.06)	0.94 (0.06)	0.057
Fasting blood glucose (mg/dl)	97 (13)	103 (19)	0.0002	97 (13)	102 (19)	0.003
2-h blood glucose (mg/dl)	122 (42)	132 (52)	0.033	120 (40)	138 (57)	0.0001
Hemoglobin A1c (%)	5.2 (0.4)	5.3 (0.6)	0.053	5.2 (0.4)	5.3 (0.6)	0.005
	Number of subjects			Number of subjects		
Smoking (packyear)						
0	440	105	0.82	436	109	0.95
1–19	17	6		19	4	
20–39	11	3		11	3	
≥ 40	1	0		1	0	
Social class						
Managerial position	20	5	0.002	21	4	0.02
Office worker	101	19		103	17	
Primary industry	23	18		26	15	
Factory worker	9	3		8	4	
Homemaker or unemployed	316	69		309	76	

*Student's t-tests for mean values and chi-squared tests for the number of subjects were performed. $n = 583$.
PD, probing pocket depth; AL, attachment loss.

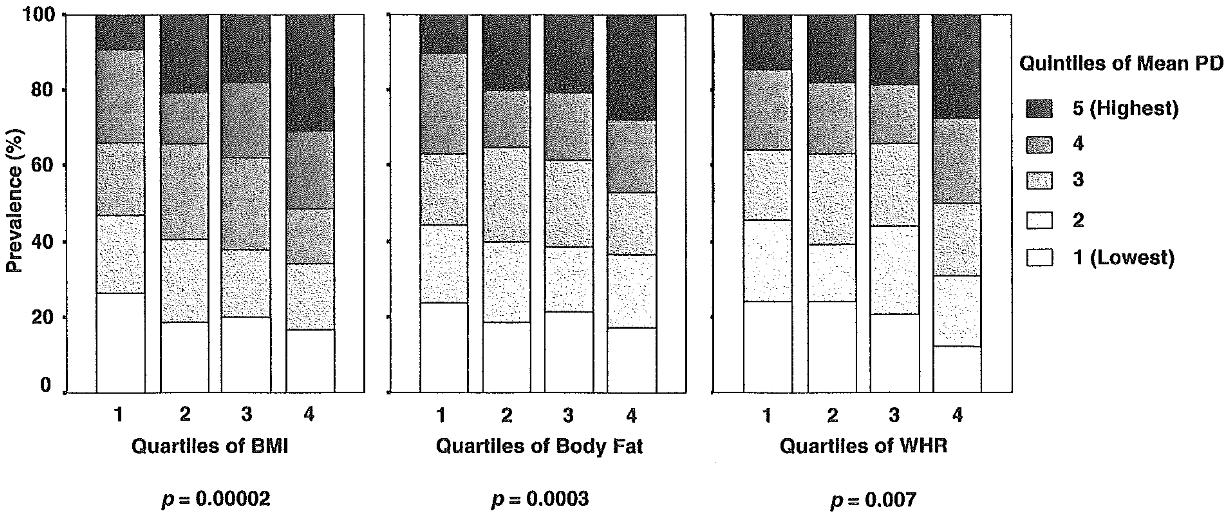

Fig. 1. Proportion of subjects with each quintile of mean probing pocket depth according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of mean probing pocket depth and the combination of lower 4 quintiles. PD, probing pocket depth; BMI, body mass index; WHR, waist–hip ratio.

shows the proportion of subjects with each quintile of mean attachment loss according to each quartile of the three obesity indexes. It is similar to Fig. 1; the highest quintile of mean attachment loss increased significantly with the quartiles of body mass index ($p = 0.02$), whereas it did not reach statistical significance when compared with the quartiles of body fat and waist–hip ratio (Fig. 2). There was a close association between every obesity

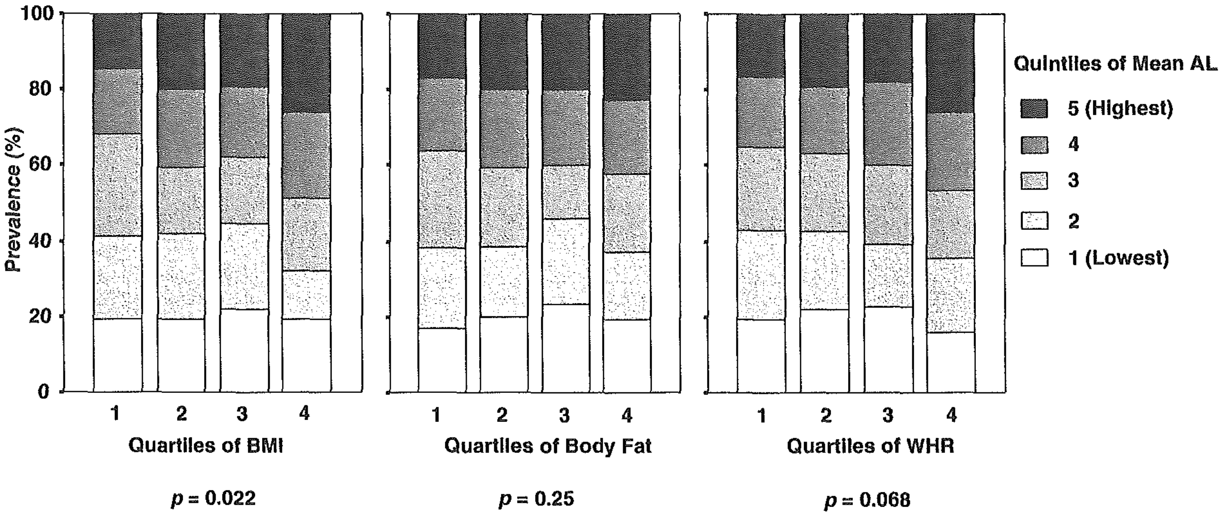

Fig. 2. Proportion of subjects with each quintile of mean attachment loss according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of mean attachment loss and the combination of lower 4 quintiles. AL, attachment loss; BMI, body mass index; WHR, waist–hip ratio.

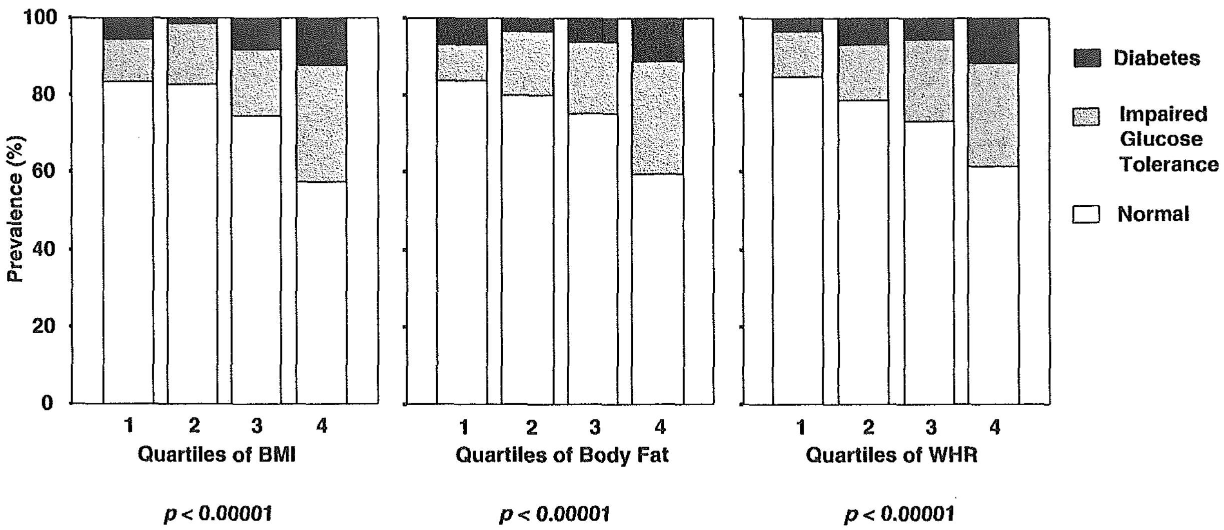

Fig. 3. Proportion of subjects with normal glucose tolerance, impaired glucose tolerance and diabetes according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between normal glucose tolerance and the combination of impaired glucose tolerance and diabetes. BMI, body mass index; WHR, waist–hip ratio.

index and the prevalence of impaired glucose tolerance and diabetes; this was to be expected, as this association is well known (Fig. 3, $p < 0.0001$). Figure 4 shows the proportion of subjects with each quintile of the mean probing pocket depth and with each quintile of the mean attachment loss, in the subjects at each glucose tolerance status. The poorer the glucose tolerance status, the greater was the proportion of subjects with the highest quintile of mean probing pocket depth ($p = 0.008$) and mean attachment loss ($p < 0.001$) (Fig. 4). Both obesity and the oral glucose tolerance test results were significantly associated with periodontal disease in these simple comparisons.

To compare the effect of obese condition and glucose tolerance condition on periodontal disease, both variables were subject to a logistic regression analysis as independent variables, simultaneously (Tables 2A–C and Tables 3A–C). A higher body mass index was significantly associated with deep pockets, adjusted for the oral glucose tolerance test results and the other risk factors of periodontal disease (Table 2A). In the multivariate analysis, subjects with the highest quartile of body mass index had a significantly

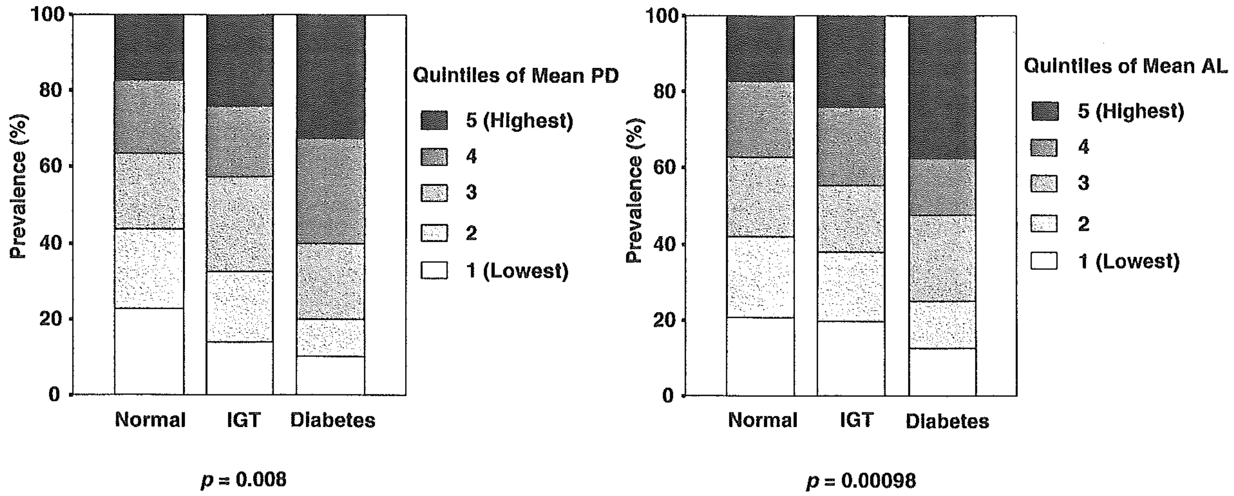

Fig. 4. Proportion of subjects with each quintile of mean probing pocket depth and with each quintile of mean attachment loss according to results of oral glucose tolerance test in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of each periodontal parameter and the combination of lower 4 quintiles. PD, probing pocket depth; AL, attachment loss; IGT, impaired glucose tolerance.

higher OR for the highest quintile of mean probing pocket depth (OR, 4.3; 95% CI, 2.1–8.9; $p < 0.001$), whereas neither impaired glucose tolerance nor diabetes were significant. In all the univariate, bivariate, and multivariate logistic regression models (Tables 2A–C), higher body mass index and body fat (highest for waist–hip ratio) were significantly associated with the highest quintile of mean probing pocket depth, even when adjusted for the oral glucose tolerance test results. The relationship between the oral glucose tolerance test results and mean probing pocket depth did not reach statistical significance when adjusted for every obesity index. Similar analyses were completed using the mean attachment loss as a dependent variable in Tables 3A–C. The results were similar to those in Tables 2A–C, although the OR of each obesity index was smaller, and was not significant, except for the crude analysis of body mass index. In the bivariate models, diabetes was significantly associated with severe attachment loss, whereas the obesity indexes were not. This differed from the results of the analysis using the mean probing pocket depth in Tables 2A–C.

Table 2A. Odds ratio for the highest quintile of mean probing pocket depth according to each quartile of body mass index and results of oral glucose tolerance test in Japanese women

	Mean PD (mm)		Odds ratio (95% CI)		
Variable	< 1.9	≥ 1.9	Univariate	Bivariate	Multivariate
BMI quartiles (kg/m^2)					
1 (15.5–20.8)	132	13	1	1	1
2 (20.8–22.7)	116	30	2.6 (1.3–5.3)†	2.7 (1.3–5.4)†	3.0 (1.4–6.3)†
3 (22.7–24.9)	120	26	2.2 (1.1–4.5)*	2.1 (1.0–4.3)*	2.3 (1.1–5.0)*
4 (25.0–46.7)	101	45	4.5 (2.3–8.8)‡	4.2 (2.1–8.2)‡	4.3 (2.1–8.9)‡
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.2 (0.7–2.1)	0.9 (0.5–1.7)
Diabetes	27	13	2.3 (1.1–4.7)*	2.0 (1.0–4.2)	1.4 (0.6–3.2)

Bivariate included BMI and OGTT as independent variables.
Multivariate included BMI, OGTT, age, plaque index, smoking history, and occupation as independent variables. $^*p < 0.05$, $^†p < 0.01$, $^‡p < 0.001$.
PD, probing pocket depth; CI, confidence interval; BMI, body mass index, OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Discussion

The relationship between obesity and deep pockets was observed after adjusting for the glucose tolerance status determined using the oral glucose tolerance test, which is used for the definitive diagnosis of diabetes (13). These results suggest that obesity is associated with deep pockets, independently of the glucose tolerance status, whereas obesity and glucose tolerance status are closely associated (Fig. 3). This suggests that the mechanism linking obesity and periodontal tissue differs from the reported mechanism operative in the effects of diabetes on the periodontium (10–12). Recent studies indicate that adipose tissue is an important organ that secretes several bioactive substances known as adipocytokines, which include tumor necrosis factor-α (19). These appear to be directly related to periodontal disease, as we discussed in a previous study (6). Although diabetes was significantly associated with both deep pockets and severe attachment loss in the crude analyses, the significant relationship between diabetes and deep pockets disappeared after adjusting for the obesity

Table 2B. Odds ratio for the highest quintile of mean probing pocket depth of each quartile of body fat and results of oral glucose tolerance test in Japanese women

	Mean PD (mm)		Odds ratio (95% CI)		
Variable	< 1.9	≥ 1.9	Univariate	Bivariate	Multivariate
Body fat quartiles (%)					
1 (7.9–24.1)	132	15	1	1	1
2 (24.2–27.9)	116	29	2.2 (1.1–4.3)*	2.2 (1.1–4.4)*	2.6 (1.2–5.3)*
3 (28.0–32.5)	116	30	2.3 (1.2–4.4)*	2.2 (1.1–4.4)*	2.8 (1.3–5.7)†
4 (32.6–52.5)	105	40	3.4 (1.8–6.4)‡	3.1 (1.6–6.0)‡	3.3 (1.6–6.8)†
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.3 (0.8–2.2)	1.0 (0.5–1.8)
Diabetes	27	13	2.3 (1.1–4.7)*	2.1 (1.0–4.4)	1.5 (0.7–3.5)

Bivariate included body fat and OGTT as independent variables.
Multivariate included Body Fat, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$.
PD, probing pocket depth; CI, confidence interval; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Table 2C. Odds ratio for the highest quintile of mean probing pocket depth of each quartile of waist–hip ratio and results of oral glucose tolerance test in Japanese women

	Mean PD (mm)		Odds ratio (95% CI)		
Variable	< 1.9	≥ 1.9	Univariate	Bivariate	Multivariate
WHR quartiles					
1 (0.75–0.89)	124	21	1	1	1
2 (0.89–0.94)	120	26	1.3 (0.7–2.4)	1.2 (0.7–2.3)	1.4 (0.7–2.8)
3 (0.94–0.97)	119	27	1.3 (0.7–2.5)	1.3 (0.7–2.4)	1.2 (0.6–2.4)
4 (0.97–1.12)	106	40	2.2 (1.2–4.0)†	2.0 (1.1–3.6)*	2.1 (1.1–4.1)*
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.4 (0.8–2.3)	1.1 (0.6–1.9)
Diabetes	27	13	2.3 (1.1–4.7)*	2.0 (1.0–4.2)	1.5 (0.7–3.4)

Bivariate included WHR and OGTT as independent variables.
Multivariate included WHR, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
PD, probing pocket depth; CI, confidence interval; WHR, waist–hip ratio; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Table 3A. Odds ratio for the highest quintile of mean attachment loss of each quartile of body mass index and results of oral glucose tolerance test in Japanese women

	Mean AL (mm)		Odds ratio (95% CI)		
Variable	< 2.42	≥ 2.42	Univariate	Bivariate	Multivariate
BMI quartiles (kg/m^2)					
1 (15.5–20.8)	124	21	1	1	1
2 (20.8–22.7)	117	29	1.5 (0.8–2.7)	1.5 (0.8–2.8)	1.6 (0.8–3.1)
3 (22.7–24.9)	118	28	1.4 (0.8–2.6)	1.3 (0.7–2.5)	1.3 (0.7–2.6)
4 (25.0–46.7)	108	38	2.1 (1,1–3.8)*	1.8 (1.0–3.3)	1.8 (0.9–3.4)
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.4 (0.8–2.3)	1.1 (0.6–1.9)
Diabetes	25	15	2.9 (1.4–5.7)*	2.7 (1.3–5.5)†	1.5 (0.7–3.2)

Bivariate included BMI and OGTT as independent variables.
Multivariate included BMI, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
AL, attachment loss; CI, confidence interval; BMI, body mass index; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

indexes (Tables 2A–C). Nevertheless, the significant relationship between diabetes and severe attachment loss remained after adjusting for the obesity indexes in the bivariate models (Tables 3A–C). In the multivariate models, the increased ORs between diabetes and both periodontal parameters did not reach statistical significance, which may be due simply to the small number of subjects, since there were only 40 diabetic subjects in this study. The oral glucose tolerance test results show the subjects' metabolic control status on that day, whereas the duration of their diabetic condition is important when studying the effects of diabetes on complications (12). Given this and the low number of subjects, this study cannot clarify the association between diabetes and periodontal disease. By contrast, impaired glucose tolerance seemed to have no association with either deep pockets or severe attachment loss in any multivariate model, despite the greater number of subjects ($n = 108$), as compared with diabetes ($n = 40$). Impaired glucose tolerance, which is an intermediate glucose condition between diabetes and normal glucose tolerance, may not have any effect on periodontal disease. This concurs with our recent report, in which deep pockets were more closely associated with the development of glucose intolerance from a normal glucose condition than with the past glucose tolerance condition itself, suggesting that deep pockets are a cause of impaired glucose tolerance (16).

In the analyses using attachment loss as a dependent variable, even the highest quartile of obesity indexes had no significant association with severe attachment loss, although the tendency was similar to the analyses using pocket depth. Although both pocket depth and attachment loss are important parameters of periodontal disease, they have slightly different meanings. A deep pocket usually means existing periodontal inflammation, whereas severe attachment loss usually represents a history of periodontal destruction, which does not always mean periodontal inflammation. Of course, the mean pocket depth and mean attachment loss are closely related ($r = 0.79$,

Table 3B. Odds ratio for the highest quintile of mean attachment loss of each quartile of body fat and results of oral glucose tolerance test in Japanese women

	Mean AL (mm)		Odds ratio (95% CI)		
Variable	< 2.42	≥ 2.42	Univariate	Bivariate	Multivariate
Body fat quartiles (%)					
1 (7.9–24.1)	122	25	1	1	1
2 (24.2–27.9)	116	29	1.2 (0.7–2.2)	1.2 (0.7–2.3)	1.3 (0.7–2.5)
3(28.0–32.5)	117	29	1.2 (0.7–2.2)	1.2 (0.6–2.1)	1.3 (0.7–2.5)
4 (32.6–52.5)	112	33	1.4 (0.8–2.6)	1.3 (0.7–2.3)	1.2 (0.6–2.3)
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.5 (0.9–2.5)	1.1 (0.6–2.0)
Diabetes	25	15	2.9 (1.4–5.7)*	2.8 (1.4–5.7)†	1.6 (0.7–3.4)

Bivariate included body fat and OGTT as independent variables.
Multivariate included body fat, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
AL, attachment loss; CI, confidence interval; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

Table 3C. Odds ratio for the highest quintile of mean attachment loss of each quartile of waist–hip ratio and results of oral glucose tolerance test in Japanese women

	Mean AL (mm)		Odds ratio (95% CI)		
Variable	< 2.42	≥ 2.42	Univariate	Bivariate	Multivariate
WHR quartiles					
1 (0.75–0.89)	121	24	1	1	1
2 (0.89–0.94)	118	28	1.2 (0.7–2.2)	1.1 (0.6–2.1)	1.2 (0.6–2.4)
3 (0.94–0.97)	120	26	1.1 (0.6–2.0)	1.0 (0.6–1.9)	1.0 (0.5–1.9)
4 (0.97–1.12)	108	38	1.8 (1.0–3.1)	1.5 (0.9–2.8)	1.3 (0.7–2.5)
OGTT					
Normal	360	75	1	1	1
IGT	82	26	1.5 (0.9–2.5)	1.4 (0.9–2.4)	1.1 (0.6–2.0)
Diabetes	25	15	2.9 (1.4–5.7)*	2.6 (1.3–5.3)†	1.5 (0.7–3.2)

Bivariate included WHR and OGTT as independent variables.
Multivariate included WHR, OGTT, age, plaque index, smoking history, and occupation as independent variables. *$p < 0.05$, †$p < 0.01$.
AL, attachment loss; CI, confidence interval; WHR, waist–hip ratio; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance.

$p < 0.0001$). Therefore, the tendencies in Tables 2A-C and 3A-C were similar and, given sufficient subjects, the relationship might reach statistical significance. Nevertheless, the weak or non-significant association between obesity and attachment loss found in this study suggests that the relationship between obesity and periodontal disease is limited to a relationship between obesity and the primary stage of periodontal disease. Since periodontal destruction, such as alveolar bone loss, is a result of inflammation, with the mechanism of the destruction arising as a consequence of inflammation (10), obesity may be related to the primary stage of periodontal disease and may not be related to the subsequent stage of periodontal destruction.

The NHANES III study found a relationship between obesity and periodontal disease in young adults only, using a combination of deep pockets and attachment loss as criteria of periodontal disease (7). As elderly people lose their teeth as a result of periodontal disease, the relationship between obesity and periodontal disease in the elderly could disappear. Since we limited the subjects of our study to those with ≥ 10 teeth, a relationship between obesity and deep pockets should be more easily detected in our study, as compared to the NHANES III study, which included subjects with fewer than 10 teeth. Although we could not analyze each age group separately, due to the small number of subjects, a relationship between obesity and deep pockets might be detected in the elderly if the subjects were to be limited to those with many teeth. Tobacco smoking is a well-documented risk factor for periodontal disease (9, 10). In this study, however, smoking history was not associated with either deep pockets or severe attachment loss, probably because there was a very low proportion of smokers among our female subjects. The prevalence of obesity is very low among Japanese as compared to the US population, whereas the prevalence of diabetes is about the same (1, 3, 12). As the effect of obesity on health is thought to differ among races, Japanese women may show different relationships between obesity, diabetes, and periodontal disease compared to other races. Since our study and other reports on the relationship between obesity and periodontal disease were cross-sectional studies, a prospective cohort study with different age groups and sexes is required.

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Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study

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Chronic kidney disease and cardiovascular disease in a general Japanese population: The Hisayama Study.

Background. Chronic kidney disease has been shown to be an independent risk factor for cardiovascular disease in high-risk populations. However, this relationship is inconclusive in community-based populations.

Methods. To clarify this issue, we followed 2634 community-dwelling individuals without cardiovascular disease, aged 40 years or older, for 12 years and examined the relationship between chronic kidney disease and the incidence of cardiovascular disease.

Results. During the follow-up period, 99 subjects (56 men and 43 women) experienced coronary heart disease, 137 subjects (60 men and 77 women) ischemic stroke, and 60 subjects (26 men and 34 women) hemorrhagic stroke. In men, the age-adjusted incidence of coronary heart disease was significantly higher in subjects with chronic kidney disease than in those without it (6.2 vs. 2.9 per 1000 person-years) ($P < 0.05$), but such a relationship was not observed with ischemic stroke. In contrast, in women, the age-adjusted incidence of ischemic stroke was significantly higher in subjects with chronic kidney disease than in those without it (3.4 vs. 2.5) ($P < 0.05$), while that of coronary heart disease was not. Chronic kidney disease was not found to be associated with the incidence of hemorrhagic stroke. In multivariate analysis, even after adjustments for traditional and nontraditional cardiovascular disease risk factors, chronic kidney disease was found to be an independent risk factor for the occurrence of coronary heart disease in men [hazard ratio (HR), 2.26; 95% CI, 1.06-4.79], and for the occurrence of ischemic stroke in women (HR, 1.91; 95% CI, 1.15-3.15).

Conclusion. Our findings suggest that chronic kidney disease is an independent risk factor for the occurrence of cardiovascular disease in the general Japanese population.

Patients with end-stage renal disease (ESRD) are at a much higher risk of cardiovascular disease than the general population, with the cardiovascular mortality rate in patients with ESRD being 10 to 20 times higher than that in general populations [1]. In 1998, the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Renal Disease issued a report emphasizing the high risk of cardiovascular disease not only in patients with ESRD, but also in those with chronic kidney disease [2]. The reason for the higher risk of cardiovascular disease in individuals with chronic kidney disease is not entirely clear, but is thought to be related in part to the high prevalence of traditional risk factors for cardiovascular disease in individuals with reduced kidney function [3]. Thus, interest has grown recently in the examination of kidney disease itself as an independent risk factor for cardiovascular disease [4, 5]. Some studies of high-risk populations, such as those who already have cardiovascular disease or who have several coexisting cardiovascular risk factors, have found decreased kidney function to be an independent risk factor for cardiovascular disease [6–20]. In prospective studies of general populations, however, the relationships between the levels of kidney function and cardiovascular disease outcomes have been inconclusive [21–25].

In the present article, we reported the findings of a prospective survey examining the relationships between cardiovascular disease and the incidence of coronary heart disease and stroke in all study subjects of a general Japanese population, taking other traditional and nontraditional risk factors into account.

Key words: chronic kidney disease, cardiovascular disease, prospective study, general populations.

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METHODS

Study population

The Hisayama Study, an epidemiologic study of cerebrovascular and cardiovascular diseases, was established in 1961 in Hisayama, a suburban community adjacent to Fukuoka City, a metropolitan area on Kyushu Island in southern Japan. Hisayama's population of approximately 7000 has been stable for 40 years. Full community surveys of the residents have been repeated since 1961 [26]. In