Cancer Causes and Control (2005) 16:573–578
DOI 10.1007/s10552-004-7839-y

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

Keiichi Tanaka*, Yutaka Kiyohara, Michiaki Kubo, Takayuki Matsumoto, Yumihiro Tanizaki, Ken Okubo, Toshiharu Ninomiya, Yoshinori Oishi, Kentaro Shikata & Mitsuo Iida
Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Received 31 May 2004; accepted in revised form 20 December 2004

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.

* Author for correspondence: Keiichi Tanaka, MD, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Maidashi 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan. Ph: +81-92-652-3080; Fax: +81-92-652-3075; E-mail: k-ichi@intmed2.med.kyushu-u.ac.jp

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.

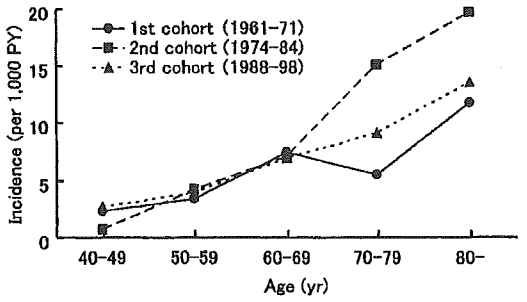

Fig. 1. The age-specific incidence of gastric cancer for men during ten-year follow-up of three Hisayama cohorts.

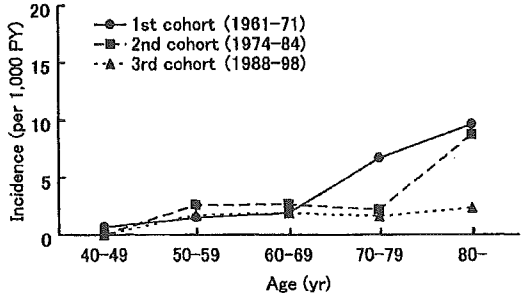

Fig. 2. The age-specific incidence of gastric cancer for women during ten-year follow-up of three Hisayama cohorts.

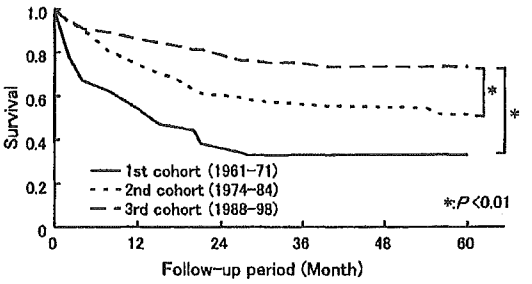

Fig. 3. Age-adjusted five-year survival curves of gastric cancer for men during ten-year follow-up in three Hisayama cohorts.

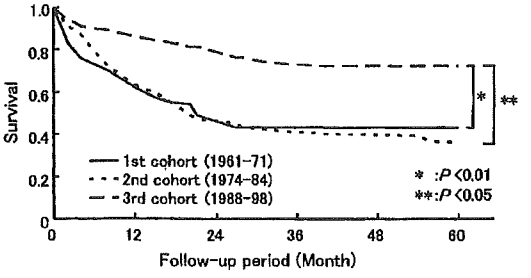

Fig. 4. Age-adjusted five-year survival curves of gastric cancer for women during ten-year follow-up in three Hisayama cohorts.

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.

Acknowledgements

This study was supported in part by a Grant-in-Aid for Scientific Research (C) (No. 13670370), a Special Coordination Fund for Promoting Science, and a Fund for Technology and Innovative Development Project in Life Sciences from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors thank the residents of Hisayama Town for their participation in the survey and the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

References

1. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J (eds.) (1997) *Cancer incidence in Five Continents.* Lyon: International Agency for Research on Cancer.
2. Lambert R, Guilloux A, Oshima A, *et al.* (2002) Incidence and mortality from stomach cancer in Japan, Slovenia and the USA. *Int J Cancer* **97**: 811–818.
3. Tominaga S (1987) Decreasing trend of stomach cancer in Japan. *Jpn J Cancer Res* **78**: 1–10.
4. Akoh JA, Macintyre IM (1992) Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. *Br J Surg* **79**: 293–299.
5. Nakamura K, Ueyama T, Yao, *et al.* (1992) Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* **70**: 1030–1037.
6. Hisamichi S (1989) Screening for gastric cancer. *World J Surg* **13**: 31–37.
7. The Research Group for Population-based Cancer Registration in Japan (1998) Cancer incidence in Japan, 1985–89: re-estimation based on data from eight population-based cancer registries. *Jpn J Clin Oncol* **28**: 54–67.
8. Hanai A, Kitagawa T, Ajika W, Tsukuma H, Oshima A (1998) Cancer incidence in Japan in 1990: estimates based on data from Population-based Cancer Registries. The Research Group for Population-based Cancer Registration in Japan. *Jpn J Clin Oncol* **28**: 450–453.
9. Schrijvers CT, Stronks K, van de Mheen DH, Coebergh JW, Mackenbach JP (1994) Validation of cancer prevalence data from a postal survey by comparison with cancer registry records. *Am J Epidemiol* **139**: 408–414.
10. Katsuki S (1966) Epidemiological and clinicopathological study on cerebrovascular disease in Japan. *Prog Brain Res* **21**: 64–89.
11. Ohmura T, Ueda K, Kiyohara Y, *et al.* (1993) Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. *Diabetologia* **36**: 1198–1203.
12. Yamagata H, Kiyohara Y, Aoyagi K, *et al.* (2000) Impact of *Helicobacter pylori* infection on gastric cancer incidence in a general Japanese population: the Hisayama study. *Arch Intern Med* **160**: 1962–1968.
13. Ueda K, Omae T, Hirota Y, *et al.* (1981) Decreasing trend in incidence and mortality from stroke in Hisayama residents, Japan. *Stroke* **12**: 154–160.
14. Fujishima M, Kiyohara Y, Kato I, *et al.* (1996) Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes*, **45**(Suppl 3): S14–S16.
15. Cox DR (1972) Regression models and life-tables. *J R Stat Soc* **34**: 187–220.
16. Kamineni A, Williams MA, Schwartz SM, Cook LS, Weiss NS (1999) The incidence of gastric carcinoma in Asian migrants to the United States and their descendants. *Cancer Causes Control* **10**: 77–83.
17. Cavelaars AE, Kunst AE, Geurts JJ, *et al.* (2000) Educational differences in smoking: international comparison. *BMJ* **320**: 1102–1107.
18. Shirota T, Magome A, Miyamoto N, *et al.* (1999) Changes of nutrient intakes and food consumption structure over a 30-years period in Hisayama. *Bulletin of Nakamura Gakuen College & Nakamura Gakuen Junior College* **31**: 141–151.

J Periodont Res 2005; 40; 346–353

JOURNAL OF PERIODONTAL RESEARCH
doi:10.1111/j.1600-0765.2005.00813.x

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

T. Saito[1], Y. Shimazaki[1], Y. Kiyohara[2], I. Kato[2], M. Kubo[2], M. Iida[2], Y. Yamashita[1]

[1]Department of Preventive Dentistry, Kyushu University Faculty of Dental Science and [2]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Saito T, Shimazaki Y, Kiyohara Y, Kato I, Kubo M, Iida M, Yamashita Y. Relationship between obesity, glucose tolerance, and periodontal disease in Japanese women: the Hisayama study. J Periodont Res 2005; 40: 346–353. © Blackwell Munksgaard 2005

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.

Toshiyuki Saito, DDS, PhD, Department of Preventive Dentistry, Kyushu University Faculty of Dental Science, Maidashi 3-1-1, Higashi-ku, Fukuoka 812–8582, Japan
Tel/Fax: +81 92 642 6352/6354
e-mail: sy@dent.kyushu-u.ac.jp

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

Accepted for publication January 19, 2005

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			Mean AL		
	< 1.9 mm $n = 469$	≥ 1.9 mm $n = 114$	p^*	< 2.42 mm $n = 467$	≥ 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 Aic (%)	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.

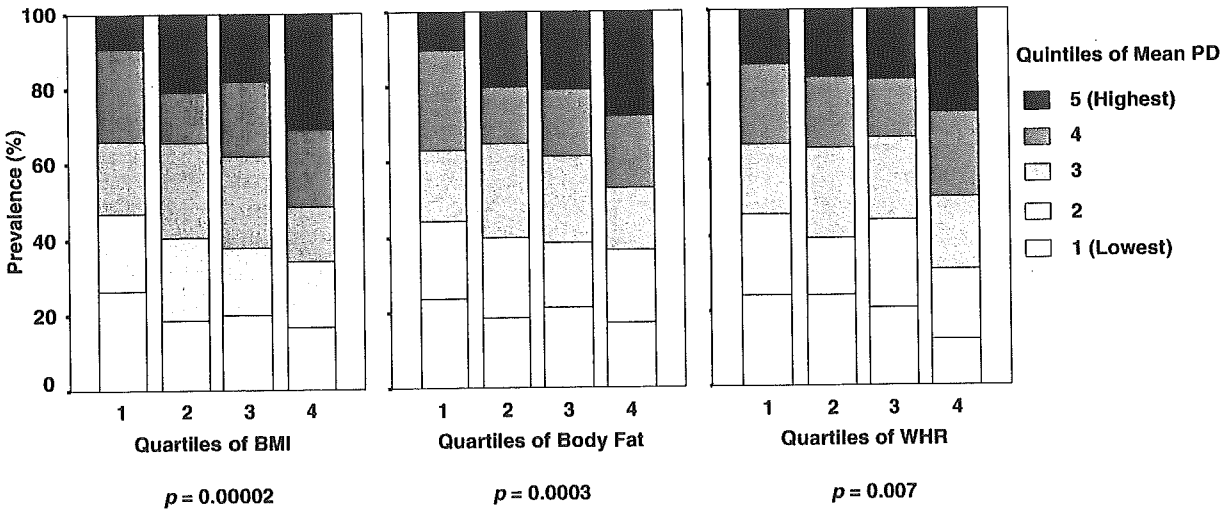

Fig. 1. Proportion of subjects with each quintile of mean probing pocket depth according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of mean probing pocket depth and the combination of lower 4 quintiles. 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

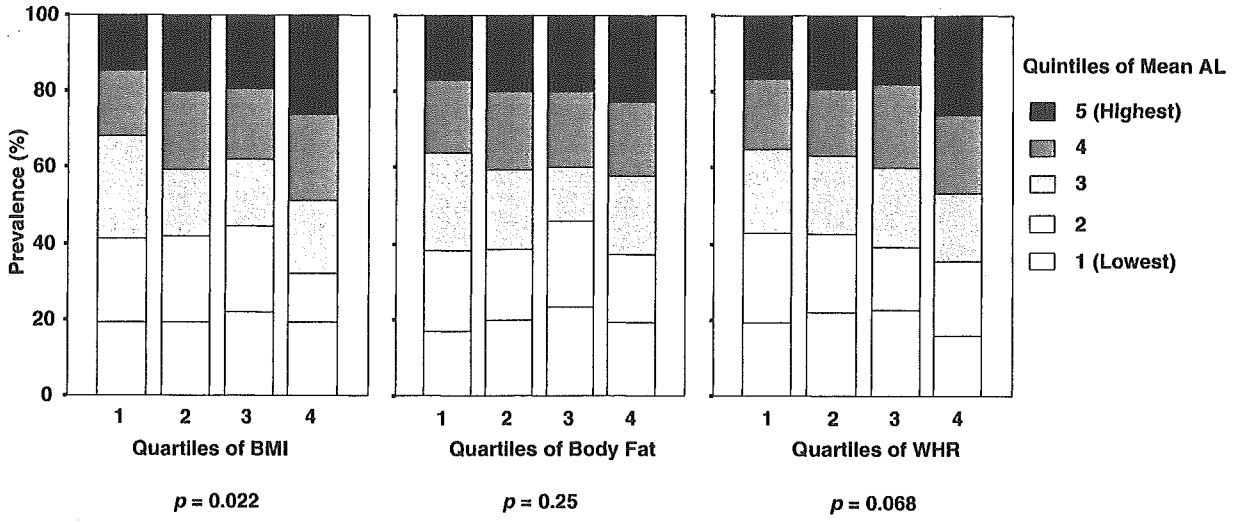

Fig. 2. Proportion of subjects with each quintile of mean attachment loss according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of mean attachment loss and the combination of lower 4 quintiles. AL, attachment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

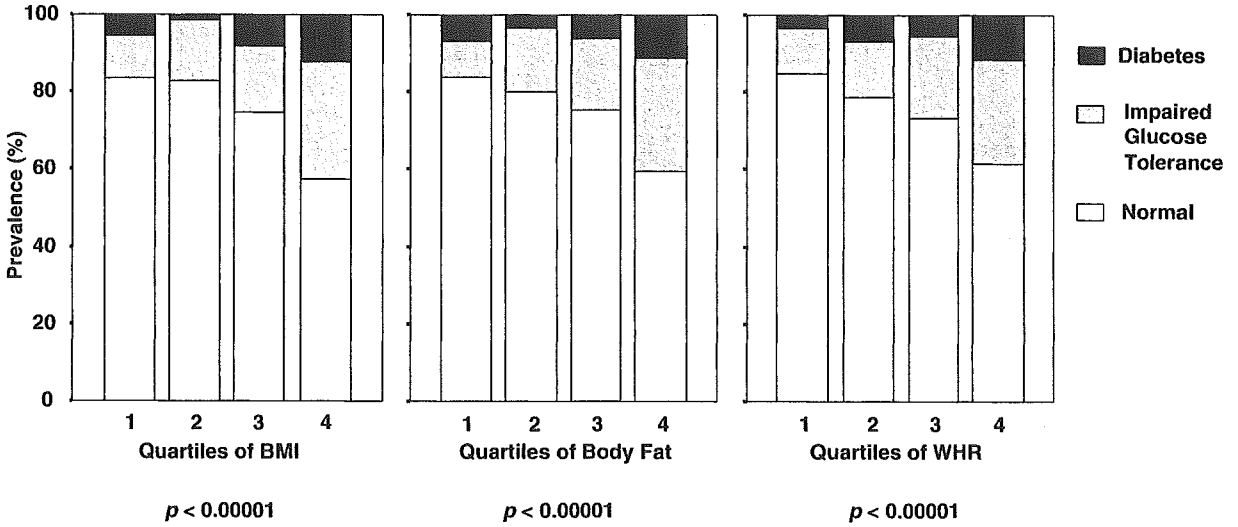

Fig. 3. Proportion of subjects with normal glucose tolerance, impaired glucose tolerance and diabetes according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between normal glucose tolerance and the combination of impaired glucose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

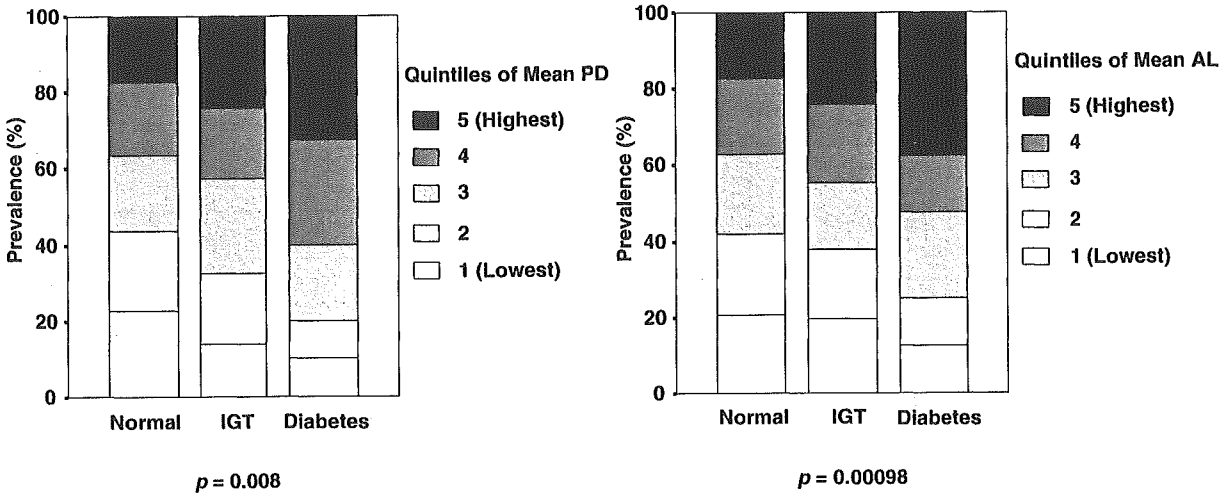

Fig. 4. Proportion of subjects with each quintile of mean probing pocket depth and with each quintile of mean attachment loss according to results of oral glucose tolerance test in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of each periodontal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

Acknowledgements

We thank Daisuke Ikeda, DDS, and Atsushi Hideshima, DDS, for periodontal examination. This work was supported in part by Grant-in-Aid of Scientific Research (Nos 15390652 and 13670370) from the Ministry of Education, Science, Sports and Culture of Japan. This article is respectfully dedicated to the memory of Toshihiko Koga, who died on 14 October 2001.

References

1. Kopelman PG. Obesity as a medical problem. *Nature* 2000;**404:**635–643.
2. Hu FB, Manson JE, Stampfer MJ *et al.* Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001;**345:**790–797.
3. Health Service Bureau, Ministry of Health and Welfare Japan. Outline of the national diabetes survey of Japan, 1997. *J Health Welfare Statistics* 1998;**45:**43–45.

4. Saito T, Shimazaki Y, Sakamoto M. Obesity and periodontitis. *N Engl J Med* 1998;**339:**482–483.
5. Saito T, Shimazaki Y, Yamashita Y, Koga T, Tsuzuki M, Sakamoto M. Association between periodontitis and exercise capacity. *Periodontal Insights* 1999;**6:**9–12.
6. Saito T, Shimazaki Y, Koga T, Tsuzuki M, Ohshima A. Relationship between upper body obesity and periodontitis. *J Dent Res* 2001;**80:**1631–1636.
7. Al-Zahrani MS, Bissada NF, Borawskit EA. Obesity and periodontal disease in young, middle-aged, and older adults. *J Periodontol* 2003;**74:**610–615.
8. Wood N, Johnson RB, Streckfus CF. Comparison of body composition and periodontal disease using nutritional assessment techniques. Third National Health and Nutrition Examination Survey (NHANES III). *J Clin Periodontol* 2003;**30:**321–327.
9. Grossi SG, Zambon JJ, Ho AW *et al.* Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *J Periodontol* 1994;**65:**260–267.
10. Page RC, Offenbacher S, Schroeder HE, Seymour GJ, Kornman KS. Advances in the pathogenesis of periodontitis: summary of developments, clinical implications and future directions. *Periodontol 2000* 1997;**14:**216–248.
11. Rees TD. Periodontal management of the patient with diabetes mellitus. *Periodontol 2000* 2000;**23:**63–72.
12. Mealey BL, Moritz AJ. Hormonal influences: effects of diabetes mellitus and endogenous female sex steroid hormones on the periodontium. *Periodontol 2000* 2003;**32:**59–81.
13. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1. diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998;**15:**539–553.
14. Kubo M, Kiyohara Y, Kato I *et al.* Effect of hyperinsulinemia on renal function in a general Japanese population: the Hisayama study. *Kidney Int* 1999;**55:**2450–2456.
15. Shimazaki Y, Saito T, Kiyohara Y *et al.* Relationship between electrocardiographic abnormalities and periodontal disease: the Hisayama Study. *J Periodontol* 2004;**75:**791–797.
16. Saito T, Shimazaki Y, Kiyohara Y *et al.* The severity of periodontal disease is associated with the development of glucose intolerance in non-diabetics: the Hisayama study. *J Dent Res* 2004;**75:**791–797.
17. Brown LJ, Brunelle JA, Kingman A. Periodontal status in the United States, 1988–1991: prevalence, extent, and demographic variation. *J Dent Res* 1996;**75**(Special Issue):672–683.
18. Silness J, Löe H. Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal condtion. *Acta Odontol Scand* 1964;**22:**121–135.
19. Shimomura I, Funahashi T, Takahashi M *et al.* Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. *Nat Med* 1996;**2:**800–803.

Kidney International, Vol. 68 (2005), pp. 228–236

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

TOSHIHARU NINOMIYA, YUTAKA KIYOHARA, MICHIAKI KUBO, YUMIHIRO TANIZAKI, YASUFUMI DOI, KEN OKUBO, YOSHIYUKI WAKUGAWA, JUN HATA, YOSHINORI OISHI, KENTARO SHIKATA, KOJI YONEMOTO, HIDEKI HIRAKATA, and MITSUO IIDA

Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

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.

Received for publication July 14, 2004
and in revised form January 6, 2005
Accepted for publication January 31, 2005

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

1988, a screening survey for the present study was performed in Hisayama. A detailed description of this survey was published previously [27]. Briefly, a total of 2736 participants aged 40 years or older (80.7% of the total population of this age group) consented to participate in the examination and underwent a comprehensive assessment. We excluded from the study 99 subjects with a history of myocardial infarction or stroke, as determined by a questionnaire and medical records. In addition, after the exclusion of one subject without a blood sample and two subjects who were on predialysis [glomerular filtration rate (GFR) <15 mL/min/1.73 m^2], the remaining 2634 individuals (1110 men and 1524 women) were enrolled in this study.

Follow-up

The subjects were followed prospectively from December 1988 to November 2000 by repeated health examinations. The health examinations were conducted yearly, and the participation rate was approximately 50% to 80%. Health status was checked yearly by mail or telephone for any subjects who did not undergo a regular examination that year or who had moved out of town. We also established a daily monitoring system among the study team and local physicians or members of the town's Health and Welfare Office. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University. During the follow-up period, 485 subjects died, of whom 366 (75.5%) underwent autopsy. Only one subject was lost to follow-up.

Definition of chronic kidney disease

GFR was estimated using the simplified prediction equation derived from the Modification of Diet in Renal Disease (MDRD) Study [28] and given by the following equation:

$$\begin{aligned} \text{GFR}(\text{mL/min/1.73m}^2) = 170 \\ \times [\text{serum creatinine (mg/dL)}]^{-0.999} \\ \times [\text{age (years)}]^{-0.176} \\ \times [\text{serum urea nitrogen (mg/dL)}]^{-0.170} \\ \times [\text{serum albumin (g/dL)}]^{0.318} \times [0.762\text{if female}] \end{aligned}$$

GFR <60 mL/min/1.73 m^2 was defined as chronic kidney disease according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines [29].

Definition of cardiovascular events

The criteria for a diagnosis of coronary heart disease included first-ever acute myocardial infarction, silent myocardial infarction, or sudden cardiac death within 1 hour after the onset of acute illness [30]. Acute myocardial infarction was diagnosed when a subject met at least two of the following criteria: (*1*) typical symptoms, including prolonged severe anterior chest pain; (*2*) abnormal cardiac enzymes more than twice the upper limit of the normal range; (*3*) evolving diagnostic electrocardiogram (ECG) changes; or (*4*) morphologic changes, including local asynergy of cardiac wall motion on echocardiography, persistent perfusion defect on cardiac scintigraphy, or myocardial necrosis or scars >1 cm long accompanied by coronary atherosclerosis at autopsy. Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal cardiac enzyme changes. During the follow-up period, we identified 99 first-ever coronary heart disease events (56 men and 43 women).

Stroke was defined as a sudden onset of nonconvulsive and focal neurologic deficit persisting for >24 hours. The diagnosis of stroke and the determination of its pathologic type were based on the clinical history, neurologic examination, all available clinical data, including brain computed tomography (CT)/magnetic resonance imaging (MRI), and autopsy findings. Stroke was classified as either ischemic or hemorrhagic [30]. Hemorrhagic stroke included cerebral hemorrhage and subarachnoid hemorrhage. During the follow-up period, we identified 197 first-ever stroke events (86 men and 111 women). These were divided into 137 cases of ischemic stroke (60 men and 77 women) and 60 cases of hemorrhagic stroke (26 men and 34 women).

Risk factors

At the baseline examination, each participant completed a self-administered questionnaire covering medical history, antihypertensive treatment, smoking habits, and alcohol intake. The completed questionnaire was checked by trained interviewers at the screening. The latter three variables were classified as either current habitual use or not. Blood pressures were measured three times, after at least 5 minutes of rest, using a standard mercury sphygmomanometer with the subject in the sitting position. The mean of three measurements was used for the analysis. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. Body height and weight were measured in light clothing without shoes, and the body mass index (kg/m^2) was calculated. Electrocardiogram (ECG) abnormalities were defined as left ventricular hypertrophy (Minnesota code, 3-1) and/or ST depression (Minnesota code, 4-1, 2, 3). The study physicians performed a physical examination of each participant and rechecked his or her medical history to improve the precision of the information. Blood samples were collected after an overnight fast for the determination of serum creatinine, urea nitrogen, albumin, hemoglobin A_{1c}, and lipids. These specimens were assayed within 24 hours. A portion of the serum

Table 1. Age-adjusted mean values or frequencies of potential risk factors and laboratory variables according to kidney function by gender

Variables	Men		Women	
	CKD (−) ($N = 1051$)	CKD (+) ($N = 59$)	CKD (−) ($N = 1313$)	CKD (+) ($N = 211$)
Age *years*	58 ± 11	73 ± 11[a]	58 ± 11	71 ± 11[a]
Serum urea nitrogen *mmol/L*	5.5 ± 1.3	7.2 ± 1.4[a]	5.2 ± 1.2	6.4 ± 1.3[a]
Creatinine *μmol/L*	94.7 (75.6-118.6)	127.8 (101.1-161.5)[a]	78.4 (63.2-97.2)	98.9 (78.7-124.2)[a]
Systolic blood pressure *mm Hg*	135 ± 19	140 ± 20	132 ± 20	138 ± 21[a]
Diastolic blood pressure *mm Hg*	80 ± 11	82 ± 12	76 ± 11	77 ± 12
Antihypertensive medication%	11.8	19.8[a]	11.5	18.9[a]
Hypertension%	42.8	60.1[b]	32.8	39.4[a]
ECG abnormalities%	19.0	17.8	12.5	9.3
Albumin *g/L*	43 ± 2	42 ± 2	42 ± 2	42 ± 2
Diabetes mellitus%	14.2	17.6	8.6	6.8
Hemoglobin A_{1c}%	5.6 ± 0.8	5.6 ± 0.8	5.5 ± 0.7	5.6 ± 0.8
Total cholesterol *mmol/L*	5.06 ± 1.06	5.46 ± 1.11[a]	5.51 ± 1.07	5.69 ± 1.14[b]
Triglycerides *mmol/L*	1.31 (0.41-4.16)	1.43 (0.43-4.77)	1.06 (0.42-2.69)	1.12 (0.42-3.00)
HDL cholesterol *mmol/L*	1.25 ± 0.31	1.25 ± 0.32	1.33 ± 0.30	1.33 ± 0.32
Body mass index kg/m^2	22.7 ± 2.9	23.1 ± 3.0	22.9 ± 3.3	23.0 ± 3.5
Total homocysteine *μmol/L*	10.4 ± 5.3	11.4 ± 5.6[a]	8.0 ± 3.7	9.8 ± 4.0[a]
HS-CRP *mg/L*	0.52 (0.02-11.50)	0.48 (0.02-12.05)	0.37 (0.02-7.69)	0.36 (0.01-8.81)
Smoking habits%	51.2	30.0	7.0	7.7
Alcohol intake%	62.0	46.6	9.7	2.9
Menopause%	—	—	64.0	67.8

Abbreviations are: CKD, chronic kidney disease; ECG, electrocardiogram; HDL, high-density lipoprotein; HS-CRP, high-sensitivity C-reactive protein.

Age is not age-adjusted. Hypertension was defined as blood pressure = 140/90 mm Hg and/or current use of antihypertensive agents. Diabetes mellitus was defined according to the criteria recommended by the American Diabetes Association by a 75 g oral glucose tolerance test in 2450 subjects (93.0%), and by a fasting and postprandial glucose concentration in 184 remainders, in addition to a medical history of diabetes. Geometric mean values and 95% confidence intervals of creatinine, triglycerides, and high-sensitivity C-reactive protein are shown due to the skewed distribution. Values are means ± standard deviations or frequencies.

[a] $P < 0.01$; [b] $P < 0.05$ vs. CKD (−).

was stored at −20°C until used in the measurement of total homocysteine and high-sensitivity C-reactive protein (HS-CRP). Serum creatinine concentrations were measured by Jaffé method. Hemoglobin A_{1c} levels were measured by the high-performance liquid chromatography (HPLC) method. The total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were all determined enzymatically. Diabetes mellitus was defined according to the criteria recommended by the American Diabetes Association [31] by a 75 g oral glucose tolerance test in 2450 subjects (93%), and by fasting and postprandial glucose concentrations in 184 remainders, in addition to a medical history of diabetes. Frozen serum samples were thawed and assayed for serum total homocysteine levels by the HPLC method and for HS-CRP by particle-enhanced technology on the Dade Behring BN II nephelometer (Dade Behring, Tokyo, Japan). A high level of HS-CRP was defined as that in the 75th percentile or higher for serum HS-CRP in either gender.

Statistical analysis

The SAS software package was used to perform all statistical analyses. Serum creatinine, triglycerides, and HS-CRP were transformed into logarithms to improve the skewed distribution. The relationships between the kidney-function category and relevant factors were tested with adjustments for age by covariance analysis or the Mantel-Haenszel chi-square test using 10-year age groupings as appropriate. The incidences of cardiovascular disease were calculated by the person-year method and adjusted for the age distribution of the World Health Organization standard population in 1998 by the direct method. Differences in incidence between the kidney function categories were tested by the Cox proportional hazards regression analysis after adjustment for age. The age- or multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were also estimated with the use of the Cox proportional hazards model. In the multivariate analysis, we selected previously reported traditional or nontraditional cardiovascular disease risk factors [3] as confounding factors, and used the stepwise method with $P < 0.2$ required for entering or remaining in the model. We confirmed the assumption of the proportional hazards model, since the log-log survivor functions by the kidney function were found to be parallel. $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

Table 1 shows the baseline clinical and demographic characteristics of the study subjects according to kidney function by gender. In either gender, the subjects with chronic kidney disease were significantly older than those without it. Thus, the mean values or frequencies of other variables were adjusted for age. The mean values of serum urea nitrogen and creatinine were significantly higher in

Table 2. Age-standardized incidence rates of cardiovascular disease according to kidney function by gender

	Men			Women		
	Person-years at risk	No. of events	Age-standardized incidence rate	Person-years at risk	No. of events	Age-standardized incidence rate
Cardiovascular disease						
CKD (−)	10,997	117	8.3	14,624	98	4.8
CKD (+)	441	17	10.7	1991	43	6.7[a]
Coronary heart disease						
CKD (−)	11,284	45	2.9	14,929	28	1.3
CKD (+)	460	11	6.2[a]	2076	15	2.7
Ischemic stroke						
CKD (−)	11,885	56	3.8	15,801	50	2.5
CKD (+)	485	4	3.1	2131	27	3.4[a]
Hemorrhagic stroke						
CKD (−)	11,885	23	1.9	15,801	30	1.4
CKD (+)	485	3	1.2	2131	4	0.8

Abbreviations are: CKD, chronic kidney disease; Incidence rate, per 1000 person-years.
[a]$P < 0.05$ vs. CKD (−).

Table 3. Age- or multivariate-adjusted analysis for occurrence of cardiovascular disease according to kidney function for men

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
Cardiovascular disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.45 (0.85–2.50)	1.29 (0.74–2.25)	1.32 (0.76–2.30)
Coronary heart disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	2.45 (1.19–5.03)[a]	2.14 (1.01–4.52)[a]	2.26 (1.06–4.79)[a]
Ischemic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	0.62 (0.22–1.77)	0.56 (0.20–1.61)	0.54 (0.19–1.53)
Hemorrhagic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.40 (0.39–5.01)	1.11 (0.29–4.21)	1.09 (0.29–4.13)

CKD is chronic kidney disease. Model 1 is adjusted for age. Model 2 is adjusted for age, systolic blood pressure, antihypertensive medication, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, and alcohol intake. Model 3 is adjusted for confounding factors used in the model 2, total homocysteine, and high-sensitivity C-reactive protein.
[a]$P < 0.05$ vs. CKD (−).

both male and female subjects with chronic kidney disease, as determined by the criteria. For both genders, subjects with chronic kidney disease had higher mean values of systolic blood pressure and higher frequencies of antihypertensive medication and hypertension. The mean total cholesterol and total homocysteine levels were also significantly higher in subjects with chronic kidney disease than in those without it in either gender. The mean values or frequencies of other potential risk factors did not differ between the two kidney function groups in either gender.

The age-standardized incidence rates of cardiovascular disease in each of the kidney function groups are shown by gender in Table 2. The cardiovascular disease incidence was higher in the subjects with chronic kidney disease than in those without it in either gender, but the difference was statistically significant only for women. The incidence of coronary heart disease was twice as high in men with chronic kidney disease as in men without it (6.2 vs. 2.9 per 1000 person-years) ($P < 0.05$), while the incidence of stroke did not differ significantly between men with chronic kidney disease and men without it. In contrast, in women the incidence of ischemic stroke was significantly higher in subjects with chronic kidney disease (3.4 vs. 2.5) ($P < 0.05$), while the incidence of coronary heart disease did not differ significantly between women with chronic kidney disease and women without it. Chronic kidney disease was not associated with hemorrhagic stroke in either gender.

Age- or multivariate-adjusted HRs of chronic kidney disease for the occurrence of cardiovascular disease were estimated for men (Table 3) and women (Table 4). The age-adjusted analysis showed that chronic kidney disease was a significant risk factor for coronary heart disease in men and for ischemic stroke in women (model 1). These relationships remained substantially unchanged even after adjustments for other traditional cardiovascular diseases risk factors, such as systolic blood pressure, antihypertensive medication, ECG abnormalities, diabetes, total cholesterol, HDL cholesterol, triglycerides, body

Table 4. Age- or multivariate-adjusted analysis for occurrence of cardiovascular disease according to kidney function for women

	Hazard ratio (95% confidence interval)		
	Model 1	Model 2	Model 3
Cardiovascular disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.55 (1.06–2.28)[a]	1.62 (1.10–2.39)[a]	1.62 (1.10–2.39)[a]
Coronary heart disease			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.58 (0.81–3.08)	1.55 (0.79–3.06)	1.55 (0.79–3.05)
Ischemic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	1.84 (1.12–3.04)[a]	1.91 (1.15–3.16)[a]	1.91 (1.15–3.15)[a]
Hemorrhagic stroke			
CKD (−)	1.00	1.00	1.00
CKD (+)	0.56 (0.19–1.67)	0.56 (0.19–1.67)	0.58 (0.19–1.73)

CKD is chronic kidney disease. Model 1 is adjusted for age. Model 2 is adjusted for age, systolic blood pressure, antihypertensive medication, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, and alcohol intake. Model 3 is adjusted for confounding factors used in the model 2, total homocysteine, and high-sensitivity C-reactive protein.

[a] $P < 0.05$ vs. CKD (−).

Table 5. Age- and gender-adjusted or multivariate-adjusted hazard ratio for occurrence of cardiovascular disease according to kidney function by status of hypertension or high-sensitivity C-reactive protein (HS-CRP) levels in 2634 subjects

	Population at risk	No. of events	Age- and sex-adjusted hazard ratio (95% CI)	Multivariate-adjusted hazard ratio (95% CI)
Hypertension (−)				
CKD (−)	1448	83	1.00	1.00
CKD (+)	91	9	1.03 (0.50-2.13)	1.11 (0.53-2.29)[a]
Hypertension (+)				
CKD (−)	916	132	1.00	1.00
CKD (+)	179	51	1.54 (1.08-2.20)[b]	1.63 (1.14-2.33)[a,c]
Low levels of HS-CRP				
CKD (−)	1806	144	1.00	1.00
CKD (+)	178	39	1.63 (1.10-2.41)[b]	1.59 (1.07-2.36)[b,d]
High levels of HS-CRP				
CKD (−)	558	71	1.00	1.00
CKD (+)	92	21	1.49 (0.88-2.54)	1.46 (0.84-2.52)[d]

Abbreviations are: CKD, chronic kidney disease; CI, confidence interval. Hypertension was defined as blood pressure ≥140/90 mm Hg and/or current use of antihypertensive agents. A high level of high-sensitivity C-reactive protein was defined as that in the 75th percentile or higher for serum high-sensitivity C-reactive protein in either gender.

[a] Adjusted for age, gender, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, alcohol intake, total homocysteine, and high-sensitivity C-reactive protein.

[b] $P < 0.05$ vs. CKD (−).

[c] $P < 0.01$.

[d] Adjusted for age, gender, systolic blood pressure, antihypertensive medication, electrocardiogram abnormalities, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, triglycerides, body mass index, smoking habits, alcohol intake, and total homocysteine.

mass index, smoking habits, and alcohol intake (model 2). Furthermore, even after controlling for nontraditional cardiovascular disease risk factors, including total homocysteine and HS-CRP, chronic kidney disease was found to be an independent risk factor for the occurrence of coronary heart disease in men (model 3) (HR 2.26 and 95% CI 1.06-4.79) ($P < 0.05$) and for the occurrence of ischemic stroke in women (HR 1.91 and 95% CI 1.15-3.15) ($P < 0.05$).

We examined the associations between GFR as a continuous variable and cardiovascular disease outcomes. This analysis showed the significant inverse association between GFR levels and the risk of coronary heart disease (CHD) events in men (for a decrease in GFR by 10 mL/min/1.73 m^2) (HR 1.30 and 95% CI 1.01-1.67) ($P < 0.05$), even after adjustments for the traditional and nontraditional cardiovascular disease risk factors named above. A similar tendency was observed for the risk of ischemic stroke in women (HR 1.26 and 95% CI 0.98-1.60) ($P = 0.07$).

There were no significant interactions between kidney function and risk factors, including hypertension, diabetes, smoking habits, ECG abnormalities, total cholesterol, triglycerides, HDL cholesterol, total homocysteine, and HS-CRP in the occurrence of cardiovascular disease.

Because hypertension and inflammation are strong risk factors for cardiovascular disease, we examined the effects of chronic kidney disease on the occurrence of cardiovascular disease stratified by hypertension or levels

of HS-CRP. As shown in Table 5, the age- and gender-adjusted or multivariate-adjusted HR of cardiovascular disease was significantly higher in the subjects with chronic kidney disease than in those without it in the hypertensive group, but not in the normotensive group. On the other hand, chronic kidney disease is a risk factor for cardiovascular disease events regardless of HS-CRP levels, though it is not significant in high levels of HS-CRP, probably because of the small number of subjects in the present study.

DISCUSSION

In a prospective study of a community-dwelling Japanese population, we demonstrated chronic kidney disease to be an independent predictor of coronary heart disease events in men and of the occurrence of cardiovascular disease and ischemic stroke in women. To our knowledge, this is the first population-based prospective study on the association between chronic kidney disease and cardiovascular disease in Japan.

The reduction in kidney function has consistently been found to be an independent risk factor for cardiovascular disease and all-cause mortality in patients after coronary events [6, 7] in those undergoing coronary interventions [8, 9], in patients with heart failure [10–12], in patients with hypertension [13–15] or diabetes [16], and in elderly subjects [17–20]. This relationship has been inconsistent, however, in prospective studies of general populations. In the Atherosclerosis Risk in Communities (ARIC) Study [21] and the Second National Health and Nutrition Examination Survey (NHANES II) [22], reduced kidney function was found to be an independent risk factor for cardiovascular disease events or all-cause mortality. These findings are in accord with those of the present study. These associations were not observed, however, in the Framingham Study [23] and the First National Health and Nutrition Examination Survey (NHANES I) [24]. Differences in the study population are a possible reason for this discrepancy; for example, African Americans were part of the ARIC Study but not of the Framingham Study. Another possible reason is that serum creatinine, which was used as a measure of renal function in both the Framingham Study [23] and the NHANES I [24], is less sensitive than estimated GFR, which was used in our study as well as in the ARIC and NHANES II Studies, in the detection of small differences in the levels of kidney function; thus, an association in low-risk populations may be less detectable when serum creatinine is used. When we examined the associations between serum creatinine and cardiovascular disease events in our population, we found no significant associations between these parameters, indicating that GFR is a better predictor of cardiovascular disease events than serum creatinine.

There are several possible explanations for the independent association of chronic kidney disease with cardiovascular disease outcome [5]. Reduced renal function is associated with a high prevalence of traditional cardiovascular disease risk factors, such as aging, diabetes, smoking habits, elevated blood pressure, and total cholesterol levels, decreased HDL cholesterol levels, and left ventricular hypertrophy by ECG [3]. In addition, a reduced GFR may be associated with increased levels of nontraditional cardiovascular disease risk factors, such as total homocysteine, inflammation, production of nitric oxide, oxidative stress, and thrombogenic factors [3, 32]. These factors could increase the risk of cardiovascular disease in subjects with chronic kidney disease. In our subjects, however, the association between chronic kidney disease and the incidence of cardiovascular disease remained significant even after adjustment for the traditional cardiovascular disease risk factors named above and some of the nontraditional cardiovascular disease risk factors, including total homocysteine and HS-CRP levels. Further investigation is needed into the role of other nontraditional cardiovascular disease risk factors in the occurrence of cardiovascular disease among subjects with chronic kidney disease. Another possible explanation for the chronic kidney disease-cardiovascular disease association is that reduced renal function may be a marker of vascular disease. In our previous autopsy study of deceased Hisayama residents, the development of renal arteriosclerosis and glomerular sclerosis was found to be closely associated with reduced GFR in both genders [33]. It is well recognized that renal arteriosclerosis and glomerular sclerosis are closely related to systemic atherosclerosis [34, 35], suggesting an increased risk of cardiovascular disease in subjects with chronic kidney disease.

In the stratified analysis, we found that chronic kidney disease was a significant predictor of cardiovascular disease in the hypertensive subjects. Previous clinical studies have also found that reduced GFR is a risk factor for cardiovascular disease events in patients with hypertension [17–19]. Because hypertension is a strong risk factor for the progression of systemic atherosclerosis, it is reasonable to consider that subjects with hypertension already have vascular injuries to some extent. Our findings, together with those of the other studies, suggest that chronic kidney disease is a marker of advanced vascular injuries in high-risk populations, or that chronic kidney disease–related metabolic disorders, such as dyslipidemia, oxidative stress, or calcium-phosphate abnormality, accelerate the progression of preexisting vascular injuries [36]. The reason why chronic kidney disease was not a significant risk factor for cardiovascular disease in the normotensive subjects may be that the causes of chronic kidney disease among normotensives, such as primary renal disease, are not directly related