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

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

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

* $P < 0.05$

† OR; odds ratio

‡ CI; confidence interval

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

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

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

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

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Abstract

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

Introduction

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

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

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

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Subjects and methods

Study population

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

Follow-up survey

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

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

Risk factors

Recumbent blood pressures were measured at every examination, and hypertension was defined as $\geq 140/90$ 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.

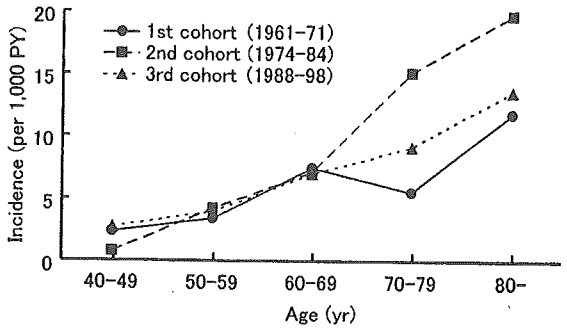

Fig. 1. The age-specific incidence of gastric cancer for men during ten-year follow-up of three Hisayama cohorts.

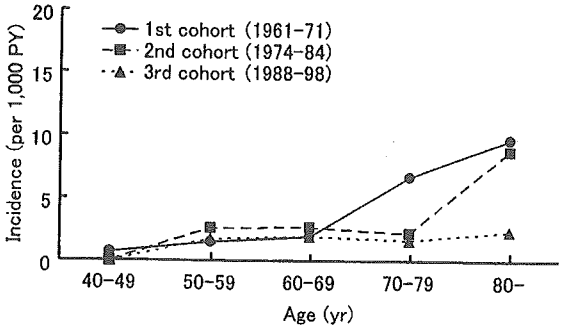

Fig. 2. The age-specific incidence of gastric cancer for women during ten-year follow-up of three Hisayama cohorts.

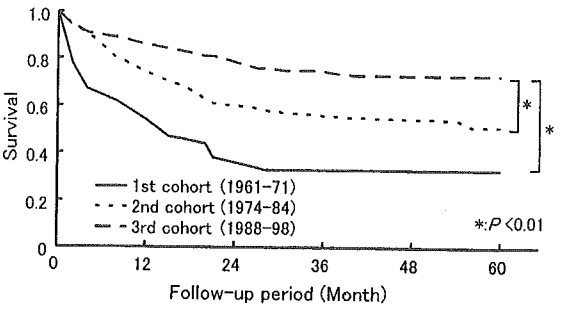

Fig. 3. Age-adjusted five-year survival curves of gastric cancer for men during ten-year follow-up in three Hisayama cohorts.

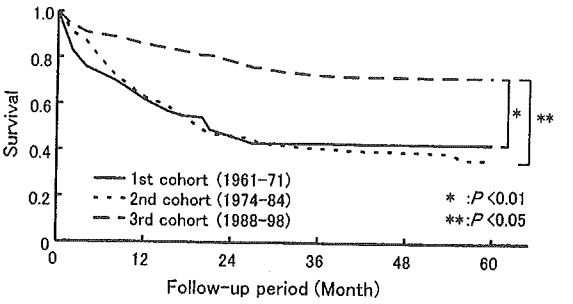

Fig. 4. Age-adjusted five-year survival curves of gastric cancer for women during ten-year follow-up in three Hisayama cohorts.

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 Drinking and Periodontitis: The Hisayama Study

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Background: Although recent studies suggest a relationship between alcohol consumption and periodontal disease, the dose-response relationship between drinking and the severity of periodontitis is unclear.

Methods: Alcohol consumption was evaluated using the frequency of drinking and the daily alcohol intake for 961 individuals aged 40 to 79 years. Periodontal status was evaluated using probing depth (PD) and clinical attachment loss (CAL).

Results: Alcohol consumption was linearly associated with the extent of PD and CAL in univariate analyses ($P<0.001$). In multivariate logistic regression analyses, the subjects drinking 15 to 29.9 g alcohol per day (odds ratio [OR] = 2.7; 95% confidence interval [CI] = 1.1 to 6.6) or more than 30 g per day (OR = 2.5; 95% CI = 1.1 to 5.7) had a significantly higher risk of having more than 35% of their teeth with PD ≥4 mm than non-drinkers, independent of other confounding variables. No significant relationship between drinking and CAL was observed in the multivariate analysis.

Conclusion: These results suggest that the effect of drinking on periodontal condition is limited to subjects with deep periodontal pockets associated with more than one-third of their teeth. *J Periodontol 2005;76:1534-1541.*

KEY WORDS

Alcoholic beverages/adverse effects; periodontitis/epidemiology; risk factors.

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Both smoking and drinking are lifestyle factors that cause health problems. Numerous studies have shown a relationship between smoking and periodontitis,[1-3] while there is very limited information about the relationship between drinking and periodontitis.[4-7] Previous studies examined the relationship between drinking and probing depth (PD)[4] or clinical attachment loss (CAL).[5] Pitiphat et al. reported a longitudinal relationship between drinking and self-reported periodontitis.[6] Recently, Nishida et al. reported that alcohol consumption is a risk indicator in subjects with the aldehyde dehydrogenase-2 ($ALDH_2$) *1/*2 genotype, but not in subjects with $ALDH_2$ *1/*1 genotype.[7] However, these studies did not find a dose-response relationship between drinking and the severity of periodontitis or conclude whether drinking has a greater effect on PD or CAL.

Drinking also affects several systemic diseases in adults, and many studies have reported J- or U-shaped associations, in which light or moderate alcohol consumption lowers the risk of hypertension,[8,9] coronary heart disease,[10,11] systemic markers of inflammation,[12] and mortality.[13] However, there are no reports on the effect of a low alcohol intake on periodontal disease. In this study, we examined the dose-response relationship between drinking and various stages of periodontal condition and examined how alcohol intake is related to periodontal condition using the results of a health examination conducted in Hisayama.

MATERIALS AND METHODS

Study Population

The Hisayama Study began in 1961 and is an ongoing population based prospective cohort study of cardiovascular diseases. The town population, based on data from national census, was shown to be representative of Japan as a whole.[14] As a part of the study, from July to September 1998, 982 Hisayama residents aged 40 to 79 years (21.6% of the total population in that age group) underwent a comprehensive health examination, including a dental examination. We excluded 21 subjects who had less than 10 teeth or lacked data for the variables studied; consequently we analyzed 961 subjects (378 male, 583 female) in this study. The Ethics Committee of Kyushu University Faculty of Dental Science and the Department of General Affairs and Health and Welfare of Hisayama approved the study design, data collection methods, and procedure for obtaining informed consent.

Oral Examination

The periodontal examination followed the method of the Third National Health and Nutrition Examination Survey (NHANES III).[15] As periodontal parameters, PD and CAL were measured at mesio-buccal and mid-buccal sites for all of the teeth present in two randomly selected quadrants: one maxillary and one mandibular. We divided the subjects into four categories according to the proportion of teeth with PD ≥4 mm. None: no teeth with PD ≥4 mm; low: 0.1% to 19.9% teeth with PD ≥4 mm; mid: 20% to 34.9% teeth with PD ≥4 mm (the second highest 10th percentile); and high: ≥35% teeth with PD ≥4 mm (the highest 10th percentile). Similarly, the proportion of teeth with CAL ≥5 mm was categorized into four categories. None: no teeth with CAL ≥5 mm; low: 0.1% to 9.9% teeth with CAL ≥5 mm; mid: 10% to 21.9% teeth with CAL ≥5 mm (the second highest 10th percentile); and high: ≥22% teeth with CAL ≥5 mm (the highest 10th percentile). Oral hygiene status was evaluated using the plaque index[16] and we used the mean score of each subject in the analyses.

General Examination

A self-administered questionnaire was completed in advance and checked by trained nurses. Participants answered items concerning their frequency of alcohol intake over the previous year and the kinds and amounts of alcoholic beverages habitually consumed. The alcohol intake per drink was converted into the weight of 100% ethanol in grams. The estimated alcohol content was 21.5 g for a cup of Japanese sake (180 ml), 22.6 g for a bottle of beer (633 ml), 35.7 g for a cup of distilled spirits (180 ml), and 31.8 g for a glass of whiskey (100 ml). The daily amount of drinking was estimated by multiplying the frequency of consuming each drink per week by the weight of ethanol in each drink and dividing the sum by seven (g/day). The daily amount of drinking was divided into four categories: non-drinker (0 g/day), light drinker (0.1 to 14.9 g/day), moderate drinker (15 to 29.9 g/day), and heavy drinker (≥30 g/day). As the number of former drinkers was very low (N = 27, 2.8%), we included past drinkers with non-drinkers. The amount of smoking, including past smoking, was given as the number of cigarettes smoked per day multiplied by the total years of smoking. The amount of smoking was divided into four categories: never smoked, light smoker (1 to 399), moderate smoker (400 to 799), and heavy smoker (≥800). Blood samples were collected from an antecubital vein after an overnight fast. Laboratory analyses of the blood samples followed previously described methods.[17] A 75 g oral glucose tolerance test was performed between 8:00 a.m. and 10:30 a.m. Before and 120 minutes after ingesting the 75 g glucose solution, blood samples were obtained for laboratory measurements. The glucose tolerance was categorized into three groups: normal (fasting and 2-hour post-challenge plasma glucose levels <110 and <140 mg/dl, respectively), diabetes (levels ≥126 or ≥200 mg/dl, respectively), and impaired (other than normal or diabetes).

Statistical Analysis

The differences in percentages were evaluated using Pearson's chi square test and its linearity was evaluated using the Mantel-Haenszel chi square test. The differences in the mean values were evaluated using Student *t* test. To protect against spurious significance with multiple inference, we used Bonferroni's correction to interpret the significance of *P* value. We performed univariate and multivariate logistic regression analyses to determine the effect of alcohol consumption on periodontal parameters, and calculated the odds ratio (OR) and 95% confidence interval (CI). As both PD and CAL were classified into four categories, we performed three logistic regression models using none versus each of the other three categories (low, mid, and high) as the dependent variable. Multivariate models were adjusted for amount of smoking, glucose tolerance, age, sex, number of teeth, and mean plaque index. The statistical analysis was performed using a software program.†

RESULTS

Tables 1 and 2 show the characteristics of the subjects according to the proportion of teeth with PD ≥4 mm and with CAL ≥5 mm, respectively. The more alcohol the subjects consumed, the greater the proportion of their teeth with PD ≥4 mm and CAL ≥5 mm,

† Version 11.0, SPSS Japan, Tokyo, Japan.

Table 1.

Study Population Variables According to Periodontal Status (PD)

Variable	Teeth With PD ≥4 mm: None 549 (57.1%)	Low 220 (22.9%)	Mid 102 (10.6%)	High 90 (9.4%)	*P* Value
	N (%)				
Alcohol consumption					
None (0 g/day)	355 (60.1)	126 (21.3)	67 (11.3)	43 (7.3)	<0.001*
Light (0.1-14.9 g/day	91 (59.1)	41 (26.6)	14 (9.1)	8 (5.2)	<0.001†
Moderate (15-29.9 g/day)	46 (50.0)	24 (26.1)	7 (7.6)	15 (16.3)	
Heavy (≥30 g/day)	57 (46.0)	29 (23.4)	14 (11.3)	24 (19.4)	
Smoking					
Never (0)	400 (62.3)	137 (21.3)	59 (9.2)	46 (7.2)	<0.001*
Light (1-399)	47 (52.8)	27 (30.3)	8 (9.0)	7 (7.9)	<0.001†
Moderate (400-799)	63 (51.6)	31 (25.4)	12 (9.8)	16 (13.1)	
Heavy (≥800)	39 (36.1)	25 (23.1)	23 (21.3)	21 (19.4)	
Glucose tolerance					
Normal	404 (60.3)	145 (21.6)	67 (10.0)	54 (8.1)	0.065*
Impaired	97 (50.8)	51 (26.7)	20 (10.5)	23 (12.0)	0.002†
Diabetes	48 (48.0)	24 (24.0)	15 (15.0)	13 (13.0)	
Gender					
Male	189 (50.0)	94 (24.9)	46 (12.2)	49 (13.0)	0.001*
Female	360 (61.7)	126 (21.6)	56 (9.6)	41 (7.0)	<0.001†
	Mean ± SD				
Age	55.6 ± 8.7	57.3 ± 8.5	59.0 ± 8.5§	55.6 ± 8.7	
Number teeth	25.6 ± 3.7	25.0 ± 3.5	23.7 ± 4.9§	23.7 ± 4.6§	
Mean plaque index	1.0 ± 0.5	1.1 ± 0.6‡	1.4 ± 0.7§‖	1.6 ± 0.7§‖	

* Non-linear component calculated using Pearson's chi square test.
† Linear component calculated using Mantel-Haenszel chi square test.
‡ $P<0.05$ compared with none; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
§ $P<0.01$ compared with none; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
‖ $P<0.01$ compared with low; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.

which was the same as when the subjects consumed more cigarettes. The subjects with poor diabetic conditions had more teeth with PD ≥4 mm and CAL ≥5 mm. The variables age, gender, number of teeth, and mean plaque index were each significantly associated with the proportion of teeth with PD ≥4 mm and CAL ≥5 mm in the univariate analyses (Tables 1 and 2).

Table 3 shows the univariate and multivariate logistic regression analyses for each of the three different PD conditions. Alcohol consumption did not show any significant influence for having the low or mid PD condition. However, moderate and heavy drinkers had a significantly high OR for having a high proportion of teeth with PD ≥4 mm in the univariate and multivariate analysis adjusting for confounding variables. In the analysis, heavy smoking and a higher plaque index also had a significantly increased OR for having the high PD condition. Table 4 (pages 1540 and 1541) shows the univariate and multivariate ORs for each of the three CAL conditions. Although moderate and heavy drinking had a significantly increased OR for having a high proportion of CAL ≥5 mm in the univariate analysis, the relationship disappeared after multivariate adjustment. Moderate and heavy smoking were associated with significantly increased OR for high CAL, and heavy smoking had a significantly increased OR for low CAL.

DISCUSSION

This study showed that subjects who drank more than 15 g alcohol per day had a significantly increased risk for widespread periodontal disease; i.e., more than one third of teeth with PD ≥4 mm, as compared to non-drinkers. Conversely, drinking did not indicate an increased risk for having less than 35% of the teeth with PD ≥4 mm. It was reported that the subjects with $ALDH_2$ *1/*2 genotype who consumed ≥33 g alcohol per day had a significantly greater percentage of PD ≥3.5 mm than those whose daily consumption was lower, while there was no significant difference in periodontal status associated with alcohol consumption in $ALDH_2$ *1/*1 subjects.[7] The subjects with $ALDH_2$ genotypes *1/*2 or *2/*2 lack $ALDH_2$ activity and become flushed after alcohol intake owing to the marked elevation in the blood acetaldehyde concentration.[18] Therefore, it is thought that drinking raises the risk of periodontitis when drinking causes an accumulation of acetaldehyde. As about half of all Japanese lack $ALDH_2$ activity,[19,20] many subjects with $ALDH_2$ *1/*2 genotype might have been included in the subjects with many teeth with PD ≥4 mm in our study.

Periodontitis is a chronic inflammatory disease of the soft and hard periodontal tissues and recent studies have suggested a relationship between periodontitis and circulatory diseases.[21-23] Inflammation plays an important role in both the initiation and pro-

Table 2.

Study Population According to Periodontal Status (CAL)

Variable	Teeth With CAL ≥5 mm: None 624 (64.9%)	Low 146 (15.2%)	Mid 95 (9.9%)	High 96 (10.0%)	*P* Value
	N (%)				
Alcohol consumption					
None (0 g/day)	394 (66.7)	85 (14.4)	65 (11.0)	47 (8.0)	0.002*
Light (0.1-14.9 g/day)	106 (68.8)	26 (16.9)	12 (7.8)	10 (6.5)	<0.001†
Moderate (15-29.9 g/day)	57 (62.0)	12 (13.0)	8 (8.7)	15 (16.3)	
Heavy (≥30 g/day)	67 (54.0)	23 (18.5)	10 (8.1)	24 (19.4)	
Smoking					
Never (0)	458 (71.3)	84 (13.1)	62 (9.7)	38 (5.9)	<0.001*
Light (1-399)	53 (59.6)	18 (20.2)	10 (11.2)	8 (9.0)	<0.001†
Moderate (400-799)	70 (57.4)	20 (16.4)	14 (11.5)	18 (14.8)	
Heavy (≥800)	43 (39.8)	24 (22.2)	9 (8.3)	32 (29.6)	
Glucose tolerance					
Normal	461 (68.8)	90 (13.4)	59 (8.8)	60 (9.0)	<0.001*
Impaired	114 (59.7)	36 (18.8)	27 (14.1)	14 (7.3)	<0.001†
Diabetes	49 (49.0)	20 (20.0)	9 (9.0)	22 (22.0)	
Gender					
Male	206 (54.5)	69 (18.3)	42 (11.1)	61 (16.1)	<0.001*
Female	418 (71.7)	77 (13.2)	53 (9.1)	35 (6.0)	<0.001†
	Mean ± SD				
Age	55.0 ± 8.6	57.7 ± 8.3‡	59.7 ± 8.2‡	59.9 ± 9.1‡	
Number of teeth	25.7 ± 3.8	25.9 ± 2.7	23.5 ± 4.4‡§	22.0 ± 4.7‡§	
Mean plaque index	1.0 ± 0.6	1.1 ± 0.6	1.2 ± 0.6‡	1.6 ± 0.6‡§‖	

* Non-linear component calculated using Pearson's chi square test.
† Linear component calculated using Mantel-Haenszel chi square test.
‡ $P<0.01$ compared with none; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
§ $P<0.01$ compared with low; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.
‖ $P<0.01$ compared with mid; Student *t* test applied with Bonferroni's correction of *P* value for type 1 errors in multiple comparisons.

gression of atherosclerosis,[24] and the systemic inflammatory marker such as C-reactive protein (CRP) is a predictor of cardiovascular events.[25] The subjects with periodontitis had a higher CRP level than the subjects with healthy periodontal tissue.[26,27] Periodontal disease was significantly associated with a higher CRP level in a longitudinal study[28] and recent studies reported that control of periodontal health decreased the serum CRP level.[29,30] Although CRP level is unknown in this study, as our results showed that moderate to heavy drinking was associated with a significant risk of having many teeth with deep PD, increased periodontal inflammation with alcohol consumption may increase the risk of coronary heart disease, in addition to the direct effect of alcohol on the circulatory system.

Tezal et al. reported a significant relationship between the frequency of drinking and CAL.[5] We did not find a significant relationship between drinking and CAL. It may be owing to small sample size, especially the low number of drinkers in this study. Alcohol is considered an important risk factor for various bone-related disorders, such as reduced bone mass and fractures, and chronic alcohol abuse is a major risk factor for osteoporosis.[31,32] A 2001 study found a relationship between osteoporosis and periodontitis in menopausal women.[33] If drinking exacerbates alveolar bone resorption, the observed effect of drinking on increasing periodontal pocket depth may lead to extensive periodontal destruction.

Some studies have reported J- or U-shaped relationship in which light drinkers had a lower risk of hypertension, coronary heart disease, systemic markers of inflammation, and mortality of all causes than did non-drinkers or heavy drinkers.[8-13] Previous studies of the relationship between drinking and periodontitis failed to find a significant association between light drinking and periodintitis, although two studies showed that light drinkers tended to have better periodontal health than non-drinkers.[5,7] In our study, although light drinkers had a relatively low risk for having many teeth with deep PD, the relationship was not significant statistically. It is thought that a large number of study subjects is needed to clarify the effect of light drinking on periodontitis.

Smoking is an important lifestyle-related risk factor for periodontitis, and this study suggests that heavy drinking is also a risk factor for periodontitis. Smoking cessation should be strongly recommended for patients with periodontitis. As our results were based on a cross-sectional investigation, we could not clarify causal relationship between drinking and periodontitis. Therefore, at this stage, we may advise heavy drinkers with periodontitis to reduce the amount they drink to improve both their systemic and oral health. In order to establish the

Table 3.

Risk for Low, Mid, and High Proportion of Teeth With PD ≥4 mm According to Alcohol Consumption and Other Variables

	Model 1				Model 2			
Independent Variable	Teeth With PD ≥4 mm None	Low	Univariate OR (95% CI)	Multivariate OR (95% CI)	Teeth With PD ≥4 mm None	Mid	Univariate OR (95% CI)	Multivariate OR (95% CI)
Alcohol consumption								
None (0 g/day)	355	126	1	1	355	67	1	1
Light (0.1-14.9 g/day)	91	41	1.3 (0.8-1.9)	1.3 (0.8-2.0)	91	14	0.8 (0.4-1.5)	0.7 (0.4-1.5)
Moderate (15-29.9 g/day)	46	24	1.5 (0.9-2.5)	1.3 (0.7-2.4)	46	7	0.8 (0.3-1.9)	0.8 (0.3-2.0)
Heavy (≥30 g/day)	57	29	1.4 (0.9-2.4)	1.1 (0.6-2.0)	57	14	1.3 (0.7-2.5)	0.7 (0.3-1.7)
Smoking								
Never (0)	400	137	1	1	400	59	1	1
Light (1-399)	47	27	1.7 (1.0-2.8)*	1.7 (0.9-3.1)	47	8	1.2 (0.5-2.6)	1.4 (0.6-3.7)
Moderate (400-799)	63	31	1.4 (0.9-2.3)	1.4 (0.7-2.5)	63	12	1.3 (0.7-2.5)	1.4 (0.6-3.5)
Heavy (≥800)	39	25	1.9 (1.1-3.2)*	1.6 (0.8-3.2)	39	23	4.0 (2.2-7.2)‡	3.5 (1.4-8.7)†
Glucose tolerance								
Normal	404	145	1	1	404	67	1	1
Impaired	97	51	1.5 (1.0-2.2)	1.4 (0.9-2.0)	97	20	1.2 (0.7-2.1)	1.0 (0.6-1.8)
Diabetes	48	24	1.4 (0.8-2.4)	1.1 (0.7-2.0)	48	15	1.9 (1.0-3.6)	1.5 (0.7-3.0)
Gender								
Male	189	94	1	1	189	46	1	1
Female	360	126	0.7 (0.5-1.0)*	1.1 (0.6-1.8)	360	56	0.6 (0.4-1.0)*	1.2 (0.6-2.7)
Age (years)			1.0 (1.0-1.0)*	1.0 (1.0-1.0)			1.0 (1.0-1.1)‡	1.0 (1.0-1.0)
Number of teeth			1.0 (0.9-1.0)*	1.0 (0.9-1.0)			0.9 (0.9-0.9)‡	1.0 (0.9-1.0)
Mean plaque index			1.5 (1.1-2.0)†	1.3 (1.0-1.7)			3.6 (2.5-5.2)‡	3.0 (2.0-4.4)‡

* $P<0.05$.
† $P<0.01$.
‡ $P<0.001$.

effect of drinking as a risk factor for periodontitis, larger-scale epidemiological and interventional studies, for example examining the effect of temperance and abstinence from drinking in heavy drinkers with periodontitis, are needed to confirm the causal relationship between drinking and periodontitis, as well as supportive experimental studies to clarify the mechanisms for the relationship between drinking and periodontitis.

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Table 3. (continued)

Risk for Low, Mid, and High Proportion of Teeth With PD ≥4 mm According to Alcohol Consumption and Other Variables

Model 3			
Teeth With PD ≥4 mm		Univariate	Multivariate
None	High	OR (95% CI)	OR (95% CI)
355	43	1	1
91	8	0.7 (0.3-1.6)	0.6 (0.3-1.6)
46	15	2.7 (1.4-5.2)†	2.7 (1.1-6.6)*
57	24	3.5 (2.0-6.2)‡	2.5 (1.1-5.7)*
400	46	1	1
47	7	1.3 (0.6-3.0)	1.2 (0.4-3.2)
63	16	2.2 (1.2-4.1)*	1.7 (0.7-4.2)
39	21	4.7 (2.5-8.6)‡	2.8 (1.1-7.3)*
404	54	1	1
97	23	1.8 (1.0-3.0)*	1.2 (0.7-2.3)
48	13	2.0 (1.0-4.0)*	1.3 (0.6-3.0)
189	49	1	1
360	41	0.4 (0.3-0.7)‡	1.7 (0.7-3.9)
		1.0 (1.0-1.0)	1.0 (0.9-1.0)
		0.9 (0.9-0.9)‡	0.9 (0.9-1.0)
		5.4 (3.6-8.0)‡	4.6 (3.0-7.0)‡

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Table 4.

Risk for Low, Mid, and High Proportion of Teeth With CAL ≥5 mm According to Alcohol Consumption and Other Variables

	Model 1				Model 2			
Independent Variable	Teeth With CAL ≥5 mm		Univariate OR (95% CI)	Multivariate OR (95% CI)	Teeth With CAL ≥5 mm		Univariate OR (95% CI)	Multivariate OR (95% CI)
	None	Low			None	Mid		
Alcohol consumption								
None (0 g/day)	394	85	1	1	394	65	1	1
Light (0.1-14.9 g/day)	106	26	1.1 (0.7-1.9)	1.0 (0.6-1.7)	106	12	0.7 (0.4-1.3)	0.6 (0.3-1.3)
Moderate (15-29.9 g/day)	57	12	1.0 (0.5-1.9)	0.7 (0.3-1.5)	57	8	0.9 (0.4-1.9)	0.6 (0.2-1.4)
Heavy (≥30 g/day)	67	23	1.6 (0.9-2.7)	0.9 (0.5-1.8)	67	10	0.9 (0.4-1.8)	0.5 (0.2-1.1)
Smoking								
Never (0)	458	84	1	1	458	62	1	1
Light (1-399)	53	18	1.9 (1.0-3.3)*	2.0 (1.0-3.9)	53	10	1.4 (0.7-2.9)	1.5 (0.6-3.5)
Moderate (400-799)	70	20	1.6 (0.9-2.7)	1.5 (0.8-3.1)	70	14	1.5 (0.8-2.8)	1.1 (0.5-2.6)
Heavy (≥800)	43	24	3.0 (1.8-5.3)‡	2.6 (1.3-5.4)*	43	9	1.5 (0.7-3.3)	0.9 (0.3-2.3)
Glucose tolerance								
Normal	461	90	1	1	461	59	1	1
Impaired	114	36	1.6 (1.0-2.5)*	1.5 (0.9-2.3)	114	27	1.9 (1.1-3.0)*	1.7 (1.0-2.9)*
Diabetes	49	20	2.1 (1.2-3.7)*	1.7 (0.9-3.1)	49	9	1.4 (0.7-3.1)	0.9 (0.4-2.0)
Gender								
Male	206	69	1	1	206	42	1	1
Female	418	77	0.6 (0.4-0.8)†	1.0 (0.5-1.7)	418	53	0.6 (0.4-1.0)†	0.5 (0.2-0.9)*
Age (years)			1.0 (1.0-1.1)†	1.0 (1.0-1.1)†			1.1 (1.0-1.1)‡	1.0 (1.0-1.1)†
Number teeth			1.0 (1.0-1.1)	1.1 (1.0-1.1)*			0.9 (0.8-0.9)‡	0.9 (0.9-1.0)†
Mean plaque index			1.4 (1.0-1.9)*	1.3 (0.9-1.7)			1.8 (1.3-2.6)‡	1.3 (0.8-1.8)

* $P<0.05$.
† $P<0.01$.
‡ $P<0.001$.

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Table 4. (continued)

Risk for Low, Mid, and High Proportion of Teeth With CAL ≥5 mm According to Alcohol Consumption and Other Variables

Model 3			
Teeth With CAL ≥5 mm		Univariate	Multivariate
None	High	OR (95% CI)	OR (95% CI)
394	47	1	1
106	10	0.8 (0.4-1.6)	0.6 (0.3-1.4)
57	15	2.2 (1.2-4.2)†	1.4 (0.6-3.3)
67	24	3.0 (1.7-5.2)‡	1.2 (0.5-2.6)
458	38	1	1
53	8	1.8 (0.8-4.1)	1.9 (0.7-5.1)
70	18	3.1 (1.7-5.7)‡	2.8 (1.2-6.8)*
43	32	9.0 (5.1-15.8)‡	4.9 (1.9-12.2)†
461	60	1	1
114	14	0.9 (0.5-1.7)	0.6 (0.3-1.1)
49	22	3.5 (2.0-6.1)‡	2.0 (1.0-3.9)*
206	61	1	1
418	35	0.3 (0.2-0.4)‡	1.0 (0.4-2.3)
		1.1 (1.0-1.1)‡	1.0 (1.0-1.1)
		0.8 (0.8-0.9)‡	0.9 (0.8-1.0)†
		4.3 (3.0-6.2)‡	2.9 (1.9-4.4)‡

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

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

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

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

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

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

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 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.

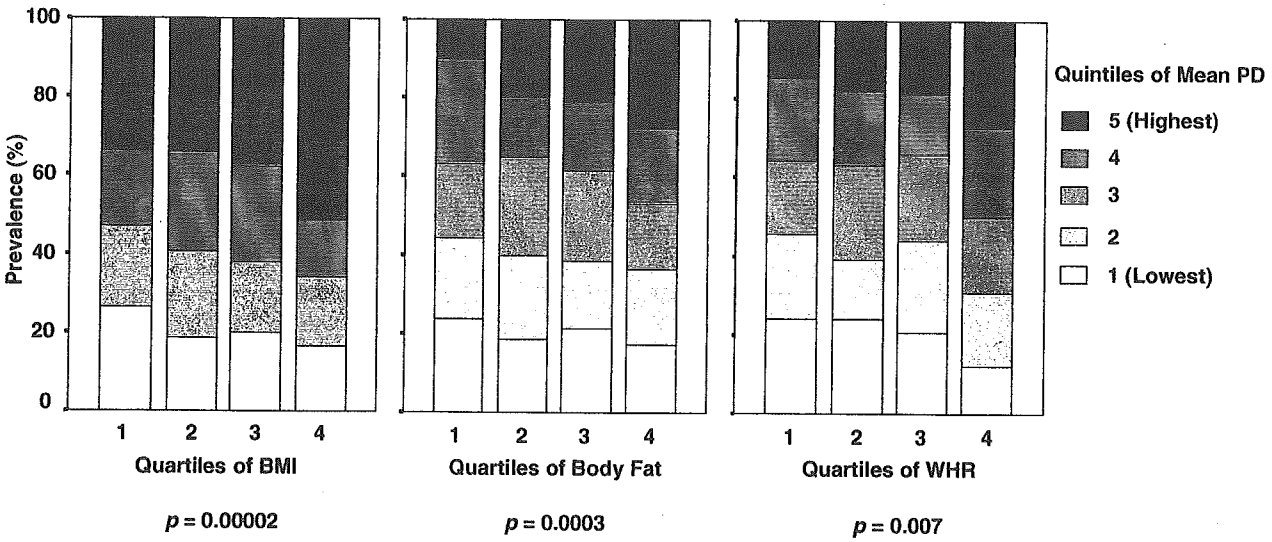

Fig. 1. Proportion of subjects with each quintile of mean probing pocket depth according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of mean probing pocket depth and the combination of lower 4 quintiles.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

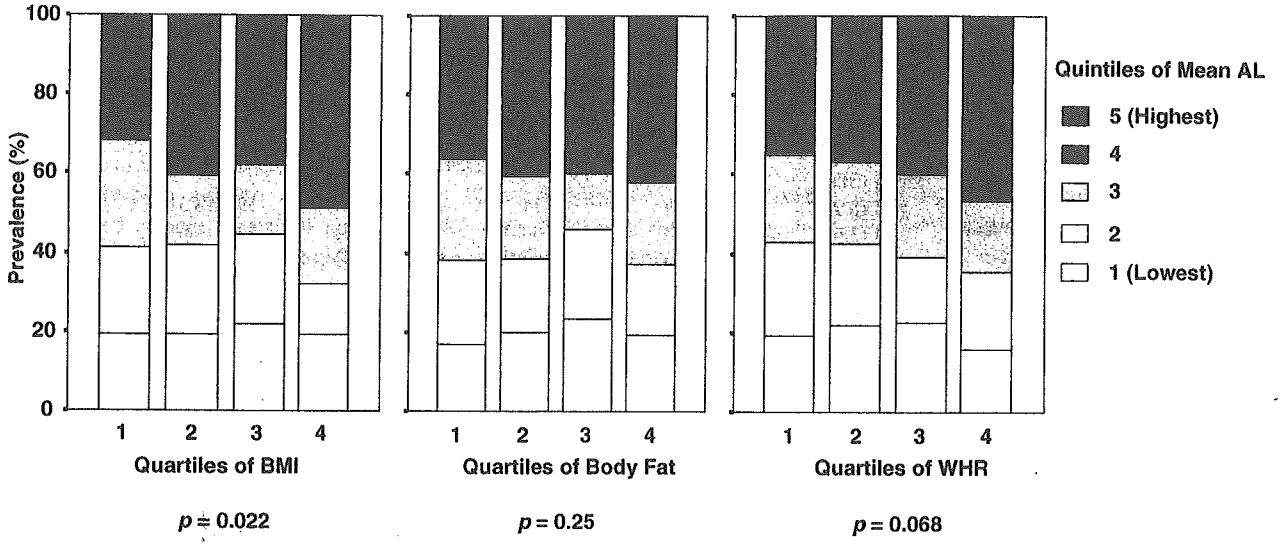

Fig. 2. Proportion of subjects with each quintile of mean attachment loss according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of mean attachment loss and the combination of lower 4 quintiles. AL, attachment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

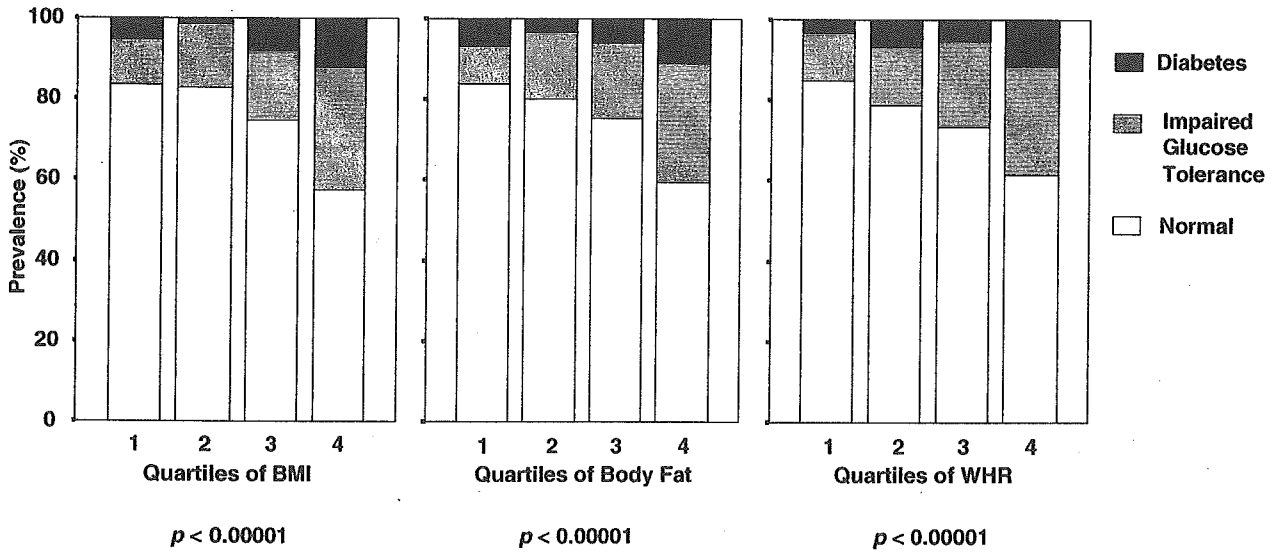

Fig. 3. Proportion of subjects with normal glucose tolerance, impaired glucose tolerance and diabetes according to quartiles of each obesity index in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between normal glucose tolerance and the combination of impaired glucose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

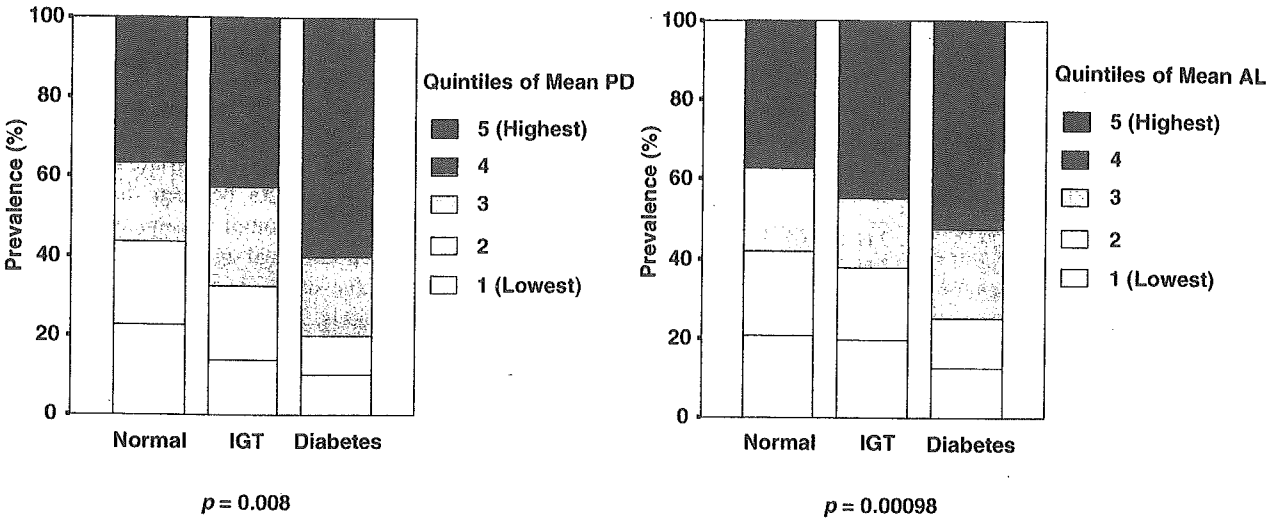

Fig. 4. Proportion of subjects with each quintile of mean probing pocket depth and with each quintile of mean attachment loss according to results of oral glucose tolerance test in Japanese women. Mantel–Haenszel chi-squared tests were performed in comparison between the highest quintile of each periodontal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