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ORIGINAL ARTICLE

Overweight and obesity trends among Japanese adults: a 10-year follow-up of the JPHC Study

Y Matsushita[1], Y Takahashi[2], T Mizoue[1], M Inoue[3], M Noda[2] and S Tsugane[3] for the JPHC Study Group

[1]*Department of Epidemiology and International Health, Research Institute, International Medical Center of Japan, Tokyo, Japan;* [2]*Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, Tokyo, Japan and* [3]*Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan*

Objective: Limited data are available regarding longitudinal changes in body weight. Here, we describe changes in the prevalences of overweight and obesity and calculated the incidence of these indices during a 10-year follow-up period for a large-scale cohort study in Japan.
Design: Longitudinal analysis of data from a population-based cohort study, the Japan Public Health Center (JPHC) Study.
Participants: A total of 65 095 Japanese men and women, who were between the ages of 40 and 69 years at baseline and participated in the 5th- and 10th-year follow-up surveys of the JPHC, were enroled in the study.
Measurements: Mean body mass index (BMI), calculated using self-reported height and weight, and the prevalences of overweight (BMI $\geqslant 25\,kg/m^2$) and obesity (BMI $\geqslant 30\,kg/m^2$) at each survey period. Incidences of overweight and obesity during the 10-year period.
Results: On an average, individuals living in Okinawa had much higher BMIs than those living on the Main islands for all sex and age groups. During the follow-up period, the prevalences of overweight and obesity steadily increased in the cohorts aged less than 50 years at baseline in both sexes. Men in younger cohorts had a higher mean BMI than those in the same age group of older cohorts, whereas the opposite trend was observed in women. The incidence of overweight individuals was greater in Okinawa than on the Main islands and among younger generations than among older ones.
Conclusion: A longitudinal analysis at the individual level showed that the prevalences of overweight and obesity increased among middle-aged Japanese participants during the follow-up period. Among men, an increasing prevalence of obesity was observed among the younger generations. These findings should be taken into consideration when planning preventive strategies for obesity and its related diseases.
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Keywords: overweight; incidence; prevalence; longitudinal study; Japan

Introduction

Obesity is a growing health problem globally, and the World Health Organization (WHO) has emphasized the importance of monitoring the prevalence and secular trends in overweight and obesity.[1] In Japan, the prevalence of obesity has been consistently increasing in men, whereas it has been stable over the last 10 years in women, according to the annual reports of the National Nutrition Survey, Japan (NNS-J); currently, the prevalence of overweight is 30.9% in men and 22.7% in women aged 20 years or older.[2]

As persons with overweight and obesity are at an increased risk of type 2 diabetes, hypertension and dyslipidemia,[3–5] there is an urgent need to establish strategies to prevent overweight and obesity. In Japan, the Ministry of Health and Welfare has initiated a project of Healthy Japan 21 to encourage changes in lifestyle,[6] and weight reduction is one of the major challenges of this project. However, as the situation has not been improving, the Ministry is now preparing an intensive lifestyle intervention at the time of annual health checkups. To establish a cost-effective preventive strategy against obesity-associated disorders, a description of the current trends and natural history of

Correspondence: Dr M Noda, Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655 Japan.
E-mail: mnoda@imcj.hosp.go.jp
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overweight and obesity would be useful to identify target populations with a greater risk of weight gain. However, to the best of our knowledge, no large-scale population-based data analyses describing longitudinal changes in body weight among the same individuals in Japan have been conducted.

The aim of this study was to describe prospectively the changes in body mass index (BMI) and the incidences of overweight and obesity in Japanese adults during a 10-year follow-up period, analyzed according to area, sex and age, using data from a large-scale population-based cohort study in Japan.

Methods

The JPHC study

The data used in this study were derived from the Japan Public Health Center (JPHC) Study, a large-scale population-based cohort study of residents in 29 administrative areas covered by a total of 11 public health centers (PHC) throughout Japan, from Okinawa to Ninohe. The JPHC Study cohort is composed of two cohorts (Cohort I: target age, 40–59 years; baseline survey, 1990; Cohort II: target age, 40–69 years; baseline survey, mainly 1993). The detailed design of the JPHC Study has been reported elsewhere.[7] This study was approved by the human ethics review committees of the National Cancer Center.

Survey

A self-administered questionnaire was distributed to all the residents in the study areas. Overall, a total of 113 403 residents (80.9%) returned the baseline questionnaire. Items included in the baseline questionnaire were sociodemographic factors, medical history, health-related lifestyles, as well as body height and body weight. Follow-up questionnaires were delivered to update the information at 5 and 10 years after the baseline study.

Tokyo–Katsushika PHC (7077 participants) and Osaka–Suita area (10 953 participants) were excluded from the analysis because participants surveyed in these areas were only those aged 40 or 50 years or selected from participants of health check-up program. Further, we excluded 1077 participants with missing information regarding height or weight at baseline, 25 606 participants who did not respond to either the 5th- or 10th-year follow-up surveys and 3595 participants with self-reported serious illness (cancer, cerebrovascular disease, myocardial infarction or chronic liver disease) at baseline or with a BMI <14 or BMI >40 at any of the three surveys. After these exclusions, 65 095 participants (29 338 men and 35 757 women) were included in the final analysis.

The self-reported BMI in the JPHC study has been validated.[8] The self-reported BMIs (mean: 23.45 kg/m^2 in men and 23.57 kg/m^2 in women) were slightly lower than the measured BMIs (mean: 23.54 kg/m^2 in men and 23.78 kg/m^2 in women), and the Spearman's correlation coefficients were high: 0.89 in men and 0.91 in women.

Analyses

We calculated BMI (kg/m^2) using the formula of self-reported weight (kg)/ height (m^2). We used the definition of overweight (BMI $\geqslant$25 kg/m^2) and obesity (BMI $\geqslant$30 kg/m^2). Because our baseline data clearly showed a higher mean BMI in Okinawa than in the Main islands and a significant difference in BMI across sex and age groups, we presented the data according to region (Main islands/Okinawa), sex and 5-year age categories.

The random effects regression model was used to examine the effect of age on BMI change during the follow-up period for each region, sex and age group, with age as the random variable. The linear regression analysis was performed to assess cohort effect on BMI for each age category in each region and sex group. Changes in the prevalences of overweight and obesity in each birth cohort were assessed by the Cochran–Mantel–Haenszel test for trend stratified by individuals, using SAS (Version 9; SAS Institute, Cary, NC, USA). As we observed the BMI only at three time points for the same individuals, the incidence of overweight was defined as a transition from a normal weight at baseline to overweight at the time of the 10th-year follow-up survey. Similarly, the incidence of obesity was defined as a change from non-obesity at baseline to obesity at the time of the 10th-year follow-up survey. To assess the potential influence of residential area and age on the incidences of overweight or obesity among each sex, a logistic regression analysis with adjustment of BMI at the baseline was used to estimate the odds ratios (95% confidence intervals) for the 10-year incidences of overweight and obesity for each study region and age category, using participants aged 55–59 years and living on the Main islands as the reference group. All analyses were performed using SPSS (Version 15.0, SPSS Inc, Chicago, USA) unless otherwise stated.

Results

Table 1 shows the baseline characteristics for each PHC area. Participants in Okinawa were on average shorter but had a similar mean weight when compared with those from the Main islands. The mean BMI was much higher in Okinawa than on the Main islands for both men and women. In Okinawa, the mean BMI values ranged between 24.2 and 24.8 kg/m^2, nearly equal to the WHO-defined cutoff for overweight, which is 25 kg/m^2. The difference in the mean BMI values for Okinawa and the Main islands appeared to be greater among men than among women.

Figure 1 shows the mean BMI values of the participants according to sex, region (Main islands/Okinawa) and 5-year age groups at baseline and at the 5th- and 10th-year follow-

Table 1 Baseline characteristics: JPHC Study

Area	Men				Women			
	No.	Height (cm)	Weight (kg)	BMI (kg/m^2)	No.	Height (cm)	Weight (kg)	BMI (kg/m^2)
Main islands								
Ninohe[a]	3004	163.6 (6.3)	63.3 (8.6)	23.6 (2.7)	3965	151.1 (5.4)	54.1 (7.4)	23.7 (2.9)
Yokote[a]	3877	164.2 (6.3)	62.8 (8.0)	23.3 (2.5)	4980	152.1 (5.1)	53.8 (7.3)	23.3 (3.0)
Nagaoka[b]	1090	162.6 (6.3)	60.0 (8.2)	22.7 (2.6)	1304	150.8 (6.0)	52.2 (6.8)	23.0 (2.7)
Mito[b]	6727	164.8 (6.2)	63.5 (8.8)	23.3 (2.7)	7482	152.3 (5.6)	54.2 (7.5)	23.4 (3.0)
Saku[a]	4133	164.8 (5.9)	62.9 (8.3)	23.2 (2.6)	4493	152.6 (5.2)	54.1 (7.2)	23.2 (2.9)
Chuo-higashi[b]	2428	164.7 (6.0)	63.0 (9.1)	23.2 (2.8)	3076	152.2 (5.4)	53.4 (7.5)	23.1 (3.1)
Kamigoto[b]	2585	164.6 (5.9)	63.7 (8.7)	23.5 (2.7)	3857	152.3 (5.4)	54.9 (8.2)	23.7 (3.2)
Okinawa								
Chubu[a]	2568	162.7 (5.8)	64.8 (9.0)	24.4 (2.9)	2955	150.3 (4.8)	54.8 (7.9)	24.2 (3.2)
Miyako[b]	2926	161.1 (6.3)	64.5 (9.3)	24.8 (2.9)	3645	150.1 (5.4)	54.7 (7.8)	24.3 (3.2)

Abbreviations: BMI, Body Mass Index. Values except numbers are the mean (s.d.) values. [a]Cohort I: baseline survey, 1990. [b]Cohort II: baseline survey, 1993.

ups. Mean BMI was much higher in Okinawa than on the Main islands in all sex and age groups. Average BMI tended to increase during the follow-up period for men and women aged 40–49 years at baseline, whereas it showed decreasing trend for older participants. This pattern of BMI change with aging was similar in both regions. With regard to cohort effect, men in younger cohorts had a higher mean BMI than men in the same age group of older cohorts, and the gap in mean BMI between the neighboring cohorts appears to be greater for men in Okinawa than those on the Main islands. In contrast, women in younger cohorts tended to have lower BMI than women in older cohorts.

Table 2 shows the 10-year changes in the prevalences of overweight and obesity according to sex, area and age. Among men aged 40–54 years and living on the Main islands, one in four were overweight at baseline; in Okinawa, nearly half the men aged 40–54 years were overweight at baseline. Among women, the highest prevalence was observed in the 55–59 year age group in both regions, although the proportion of overweight women in Okinawa was approximately 10% higher than that of women living on the Main islands across all the age groups. During the 10-year follow-up period, the prevalence of overweight or obesity increased in the cohorts of men and women who were in their 40s at baseline, especially those between the ages of 40–44 years. In contrast, a decreasing trend in the prevalence of overweight individuals was observed among the generations that were in their 60s at baseline.

Next, we compared the prevalence of overweight and obesity in the same age category among different age cohorts for the three surveys. For example, the prevalences of overweight among men aged 50–54 years and living on the Main islands were 26.0, 26.3 and 29.4% at the time of the baseline, 5th-year and 10th-year follow-up surveys, respectively. This comparison shows that the prevalences of overweight and obesity increased both among men on the Main islands and in Okinawa. However, the prevalences of overweight among women living on the Main islands decreased, whereas this decreasing trend was restricted to women between the ages of 50–54 years in Okinawa.

Table 3 shows the 10-year incidence of overweight and obesity according to sex, age and area, together with the odds ratios for the incidences for each study region and age category, using participants aged 55–59 years and living on the Main islands as a reference group. In general, higher incidences and greater odds ratios were consistently observed among younger generations of both men and women, irrespective of the study region, although there was a large difference in the absolute value. Among men aged 40–49 years who had a BMI $<25\,kg/m^2$ at baseline, nearly 10% of those living on the Main islands became overweight during the 10-year period, whereas nearly 20% living in Okinawa became overweight. A similar regional difference was also observed among women.

Discussion

This is the first report describing the changes in the prevalences and incidences of overweight and obesity in a large adult population in Japan utilizing the data sets from the JPHC Study. Our data for the Main island areas were comparable with the NNS-J data[9] in terms of the prevalence of overweight. The prevalences of overweight and obesity among the younger generations increased continuously during the follow-up period, whereas it decreased among the older generations. These changes seemed to parallel the changes in the BMI levels of each generation. The incidence of overweight and obesity in the 10th-year survey was greater among the younger generations than among the older ones and among individuals living in Okinawa than among individuals living on the Main islands. The prevalence of obesity is much lower in Asia (2.2–6.8%) than in the United States (30.0%).[10] Although cross-national comparisons are subject to inherent limitations, the prevalence

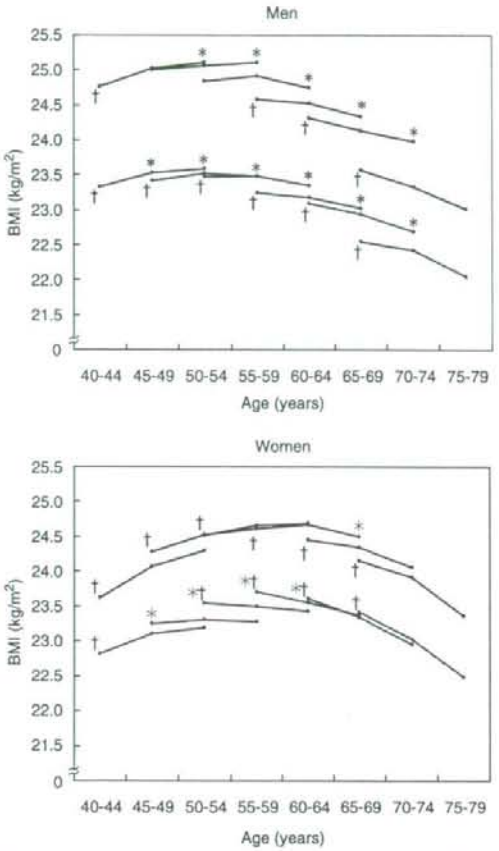

Figure 1 Changes in mean body mass index during a 10-year follow-up period. Each line shows the changes of mean BMI during the 10-year period for each birth cohort stratified by sex, region and age at baseline (Blue lines: Main islands, Red lines: Okinawa). Age effect on BMI for each birth cohort was tested by using a random effects model (* denotes $P<0.05$). Cohort effect on BMI for each age category was tested by using the linear regression analysis († denotes $P<0.05$). Standard deviation of BMI ranged between 2.6 and 3.3 for men and 2.9 and 3.7 for women.

of obesity on the Main islands appears to fall near the middle of the range for Asian countries, whereas the prevalences of overweight and obesity in Okinawa appear to be higher than those in other Asian countries.

The prevalence of obesity has been increasing among both men and women in many countries, including the United States,[11,12] Canada,[13,14] the United Kingdom,[15] most countries in the European Union[16] and Finland.[17] However, our data (Figure 1) showed that the prevalences of overweight and obesity have increased among men aged 50–69 years but tended to decrease among women in this age group. This discrepant trend in obesity among Japanese women may be a unique feature that has not been reported in western populations.

The variation in the changes of obesity index with aging across sex and age groups could be ascribed to lifestyle, social and biological factors. Diet, physical activity, smoking and drinking are known to be associated with BMI or weight change,[18–20] and these factors differ notably across sex and age groups.[9] For women, a large weight increase after menopause could be because of the change in hormone levels.[21] Factors that control eating behaviors may also have contributed to the difference. For instance, in a national survey in Japan,[22] younger non-obese women were more likely to regard themselves as overweight than older non-obese women, suggesting a differential body image across generations. Further study is needed to clarify the factors that have contributed to the different patterns of obesity trends in Japan.

The incidences of overweight and obesity have been reported for non-Asian populations. In the Framingham Study, the incidence of overweight, defined as a BMI equal to or greater than 25 kg/m^2 but less than 30 kg/m^2, increased twofold, whereas that of obesity increased more than threefold over the five decades from 1950 to 2000.[23] In two rural areas in northern Sweden and the United States, the 10-year incidence of obesity during the 1990s was 12 and 17.3%, respectively.[24] In the US First National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, the 10-year incidence of obesity among women aged 30–55 years, where obesity was defined as a BMI equal to or greater than 29 kg/m^2, was 15.5% in blacks and 9.7% in whites.[25] In the present Japanese population, the incidence of obesity was much lower than those in the western studies.

Another noticeable finding of this study was the much higher prevalences and incidences of overweight and obesity in Okinawa. Some data exist that could explain the epidemic of obesity in Okinawa. A study identified a unique dietary pattern in Okinawa, with so-called 'westernized foods'—including bread, beef and coffee—consumed more frequently in this region.[26] Moreover, the proportion of energy intake from fat was estimated to be about 30% in Okinawa, which is among the highest levels in Japan,[27] whereas the mean daily number of steps walked in Okinawa was among the lowest in the country.[27] A high-energy, high-fat dietary pattern, in combination with low physical activity levels, might have contributed to the current high prevalence of obesity in Okinawa.

The prefectural ranking of life expectancy for Okinawan men has been falling during the last 20 years, whereas that for Okinawan women remains the first.[28,29] According to a report on this issue,[30] mortality rate has increased from 1980's to 1990's in Okinawan men aged 40–49 years, whose major causes of death included cardiovascular disease, cerebrovascular disease, liver disease and diabetes mellitus; in contrast, there was no measurable change in mortality for their counterparts in the Main islands. In women, no such

Table 2 Changes in prevalences (%) of overweight and obesity during the follow-up period

		Overweight[a]				*Obesity*[a]			
Age (years) at baseline	*No.*	*Baseline*	*Fifth year*	*10th year*	*Trend P*[b]	*Baseline*	*Fifth year*	*10th year*	*Trend P*[b]
Men									
Main islands									
40–44	5826	25.0	27.7	29.4	<0.0001	1.7	1.9	2.1	0.02
45–49	4869	24.9	26.3	26.6	0.001	1.7	1.7	2.1	0.03
50–54	4781	26.0	25.9	25.7	0.39	1.5	1.5	1.3	0.21
55–59	5017	23.5	23.6	22.8	0.15	1.3	1.1	1.0	0.03
60–64	1947	21.7	21.5	19.7	0.011	1.2	1.3	1.5	0.29
65–69	1404	16.8	16.5	14.7	0.012	0.5	0.6	0.6	0.73
Okinawa									
40–44	1151	45.5	48.1	49.1	0.005	5.6	6.4	7.2	0.008
45–49	999	46.4	48.4	48.9	0.02	4.6	5.1	4.7	0.87
50–54	1129	45.2	46.1	43.1	0.07	4.8	4.6	5.2	0.46
55–59	1223	42.8	42.0	39.0	0.001	4.0	4.3	4.2	0.76
60–64	587	35.9	35.3	34.4	0.34	3.4	2.9	3.9	0.39
65–69	405	26.7	24.4	22.2	0.01	1.7	2.0	1.7	1.00
Women									
Main islands									
40–44	6422	19.9	23.7	25.3	<0.0001	1.9	2.2	2.5	<0.0001
45–49	5889	24.7	25.2	26.0	0.006	1.9	1.9	2.3	0.02
50–54	6165	28.3	28.0	28.5	0.65	2.8	2.5	2.9	0.63
55–59	6194	30.7	29.5	27.8	<0.0001	3.0	2.8	2.5	0.007
60–64	2545	30.1	28.4	24.7	<0.0001	3.1	2.2	2.1	0.000
65–69	1942	28.4	26.2	20.8	<0.0001	2.9	2.7	2.6	0.24
Okinawa									
40–44	1455	26.3	32.1	36.2	<0.0001	3.5	4.9	5.3	0.0002
45–49	1128	35.8	38.7	41.0	<0.0001	4.6	6.7	6.6	0.0003
50–54	1325	40.2	42.6	42.5	0.03	5.3	6.0	6.3	0.06
55–59	1382	41.3	42.9	40.9	0.62	6.1	5.6	5.4	0.25
60–64	759	40.3	39.1	35.3	0.0002	6.1	5.1	5.1	0.18
65–69	551	36.7	33.9	29.0	<0.0001	4.5	4.9	4.0	0.50

[a]Overweight: BMI $\geq 25\,kg/m^2$, Obesity: BMI $\geq 30\,kg/m^2$. [b]Cochran–Mantel–Henszel Test.

discrepancy in mortality trend by region was observed. As shown in Figure 1, there was an increasing gap of BMI levels between Okinawa and Main islands toward younger generation in men, but not in women. Therefore, we speculate that one of the major reasons for the falling in the ranking of life expectancy in Okinawan men could be an increase of obesity-related diseases among new generations.

Although the incidence of overweight was much higher in Okinawa, changes in the mean BMI levels during the follow-up period did not materially differ between the Main islands and Okinawa. A plausible explanation for this discrepancy is that as the participants in Okinawa had a higher mean BMI at baseline, their BMI levels would be distributed more closely to the cutoff value of overweight among those with a normal BMI than among the participants from the Main islands, so even a slight increase in weight would lead to a greater increase in the incidence of overweight in Okinawa. It would be of interest to track BMI from childhood through to middle age to identify the causes of the higher prevalences of overweight and obesity in Okinawa.

Our study has some limitations. First, the BMI levels at baseline or the subsequent changes in BMI may have differed between those who responded to all of the follow-up surveys and those who did not. We confirmed that the mean baseline BMI did not differ between the two groups in both men and women. However, we cannot deny the possibility that healthier people may have tended to participate in the follow-up surveys, which would have led to an underestimation of the incidence of overweight or obesity. Second, the use of self-reported heights and weights is a source of concern. However, the validity assessed against measured values was reasonably high,[8] and self-reported anthropometric data have been used in large-scale studies on this issue.[31] Lastly, the participants of this study were not randomly chosen from among the entire Japanese population. However, as our prevalence data for the Main islands were similar to those from NNS-J, the present results for the Main islands may be generalized to represent the Japanese population.

In conclusion, this study revealed that a sizable proportion of people under 50 years of age shifted from normal weight to overweight during a 10-year period starting in the early 1990s in Japan. Considering the higher baseline BMI in men for that age group, population approaches for weight control

Table 3 Incidences of overweight and obesity at the 10th-year follow-up survey

	Overweight[a]				*Obesity*[a]			
	No.[b]	*No. of incidence*	*Incidence (%)*	*OR (95% CI) adjusted for baseline BMI*	*No.*[c]	*No. of incidence*	*Incidence (%)*	*OR (95% CI) adjusted for baseline BMI*
Men								
Main islands								
40–44	4371	546	12.5	1.66 (1.42–1.94)	5728	60	1.0	2.46 (1.44–4.20)
45–49	3655	365	10.0	1.12 (0.95–1.33)	4786	55	1.1	2.92 (1.70–5.01)
50–54	3536	322	9.1	1.00 (0.84–1.18)	4708	37	0.8	1.80 (1.02–3.18)
55–59	3837	325	8.5	1.00 (reference)	4950	19	0.4	1.00 (reference)
60–64	1525	106	7.0	0.82 (0.65–1.05)	1923	15	0.8	2.25 (1.11–4.54)
65–69	1168	66	5.7	0.75 (0.56–1.01)	1397	4	0.3	1.14 (0.38–3.44)
Okinawa								
40–44	627	137	21.9	2.62 (2.06–3.35)	1087	40	3.7	4.84 (2.72–8.62)
45–49	535	98	18.3	1.66 (1.27–2.16)	953	20	2.1	2.12 (1.10–4.07)
50–54	619	80	12.9	1.14 (0.86–1.50)	1075	28	2.6	3.01 (1.64–5.55)
55–59	700	86	12.3	1.14 (0.87–1.50)	1174	27	2.3	2.76 (1.49–5.11)
60–64	376	43	11.4	0.96 (0.67–1.38)	567	8	1.4	2.17 (0.92–5.15)
65–69	297	21	7.1	0.71 (0.44–1.15)	398	3	0.8	1.79 (0.51–6.32)
Women								
Main islands								
40–44	5141	587	11.4	2.11 (1.82–2.46)	6301	78	1.2	2.35 (1.64–3.39)
45–49	4435	420	9.5	1.37 (1.17–1.61)	5777	61	1.1	1.50 (1.03–2.19)
50–54	4420	391	8.8	1.16 (0.99–1.36)	5991	67	1.1	1.34 (0.93–1.94)
55–59	4294	355	8.3	1.00 (reference)	6011	57	0.9	1.00 (reference)
60–64	1778	104	5.8	0.68 (0.53–0.86)	2467	15	0.6	0.64 (0.36–1.16)
65–69	1390	59	4.2	0.51 (0.38–0.68)	1885	19	1.0	1.15 (0.67–1.98)
Okinawa								
40–44	1072	190	17.7	3.02 (2.44–3.74)	1404	43	3.1	3.56 (2.30–5.53)
45–49	724	119	16.4	2.13 (1.66–2.72)	1076	33	3.1	2.73 (1.71–4.36)
50–54	793	118	14.9	1.63 (1.28–2.08)	1255	38	3.0	2.66 (1.71–4.14)
55–59	811	104	12.8	1.48 (1.15–1.91)	1298	29	2.2	1.53 (0.95–2.47)
60–64	453	41	9.1	1.02 (0.71–1.46)	713	10	1.4	0.99 (0.49–2.00)
65–69	349	25	7.2	0.78 (0.50–1.22)	526	9	1.7	1.58 (0.75–3.32)

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio. [a]Overweight: BMI $\geqslant 25\,kg/m^2$, Obesity: BMI $\geqslant 30\,kg/m^2$. [b]Number of normal weight participants at baseline. [c]Number of non-obese participants at baseline.

should be mainly targeted at men in their 40s or younger. Further studies must be performed to elucidate the factors that promote and prevent weight gain in this age group.

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Appendix

Members of the Japan Public Health Center-based Prospective Study (JPHC Study, principal investigator: S Tsugane) Group are: S Tsugane, M Inoue, T Sobue and T Hanaoka, National Cancer Center, Tokyo, Japan; J Ogata, S Baba, T Mannami, A Okayama and Y Kokubo, National Cardiovascular Center, Osaka, Japan; K Miyakawa, F Saito, A Koizumi, Y Sano, I Hashimoto, T Ikuta and Y Tanaba, Iwate Prefectural Ninohe Public Health Center, Iwate, Japan; Y Miyajima, N Suzuki, S Nagasawa, Y Furusugi and N Nagai, Akita Prefectural Yokote Public Health Center, Akita, Japan; H Sanada, Y Hatayama, F Kobayashi, H Uchino, Y Shirai, T Kondo, R Sasaki, Y Watanabe, Y Miyagawa and Y Kobayashi, Nagano Prefectural Saku Public Health Center, Nagano, Japan; Y Kishimoto, E Takara, T Fukuyama, M Kinjo, M Irei and H Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa, Japan; K Imoto, H Yazawa, T Seo, A Seiko, F Ito, F Shoji and R Saito, Katsushika Public Health Center, Tokyo, Japan; A Murata, K Minato, K Motegi and T Fujieda, Ibaraki Prefectural Mito Public Health Center, Ibaraki, Japan; K Matsui, T Abe, M Katagiri and M Suzuki, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata, Japan; M Doi, A Terao, Y Ishikawa and T Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Kochi, Japan; H Sueta, H Doi, M Urata, N Okamoto and F Ide, Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki, Japan; H Sakiyama, N Onga, H Takaesu and M Uehara, Okinawa Prefectural Miyako Public Health Center, Okinawa, Japan; F Horii, I Asano, H Yamaguchi, K Aoki, S Maruyama, M Ichii and M Takano, Osaka Prefectural Suita Public Health Center, Osaka, Japan; Y Tsubono, Tohoku University, Miyagi, Japan; K Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita, Japan; Y Honda, K Yamagishi, S Sakurai and N Tsuchiya, Tsukuba University, Ibaraki, Japan; M Kabuto, National Institute for Environmental Studies, Ibaraki, Japan; M Yamaguchi, Y Matsumura, S Sasaki and S Watanabe, National Institute of Health and Nutrition, Tokyo, Japan; M Akabane, Tokyo University of Agriculture, Tokyo, Japan; T Kadowaki, Tokyo University, Tokyo, Japan; M Noda and T Mizoue, International Medical Center of Japan, Tokyo, Japan; Y Kawaguchi, Tokyo Medical and Dental University, Tokyo, Japan; Y Takashima and M Yoshida, Kyorin University, Tokyo, Japan; K Nakamura, Niigata University, Niigata, Japan; S Matsushima and S Natsukawa, Saku General Hospital, Nagano, Japan; H Shimizu, Sakihae Institute, Gifu, Japan; H Sugimura, Hamamatsu University, Shizuoka, Japan; S Tominaga, Aichi Cancer Center Research Institute, Aichi, Japan; H Iso, Osaka University, Osaka, Japan; M Iida, W Ajiki and A Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka, Japan; S Sato, Chiba Prefectural Institute of Public Health, Chiba, Japan; E Maruyama, Kobe University, Hyogo, Japan; M Konishi, K Okada and I Saito, Ehime University, Ehime, Japan; N Yasuda, Kochi University, Kochi, Japan; and S Kono, Kyushu University, Fukuoka, Japan.

Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan

Manami Inoue[a], Mitsuhiko Noda[b], Norie Kurahashi[a], Motoki Iwasaki[a], Shizuka Sasazuki[a], Hiroyasu Iso[c], Shoichiro Tsugane[a] and for the Japan Public Health Center-based Prospective Study Group

The impact of metabolic factors, which are major risk factors for cardiovascular disease, on total cancer risk has not been clarified. We prospectively examined whether metabolic factors and their aggregates predict the subsequent occurrence of total and major sites of cancer in the Japan Public Health Center-based Prospective Study. A total of 27 724 participants (9548 men and 18 176 women) aged 40–69 years participating in a questionnaire and health checkup survey in 1993–1995 were followed for total cancer incidence through 2004. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated for metabolic factors and for two criteria of their aggregates (three or more than three factors and two or more than two additional factors in addition to being overweight) with a Cox proportional hazards model to control for potential confounding factors. In both sexes, the presence of metabolic factors in the aggregate did not predict subsequent occurrence of cancer as a whole. By site, a significant increase in risk was observed for male liver cancer [HR=1.73, CI=1.03–2.91 (three or more than three factors); HR=1.99, CI=1.11–3.58 (two or more than two additional factors in addition to being overweight)], and female pancreatic cancer [HR=1.99, CI=1.00–3.96 (two or more than two additional factors in addition to being overweight)]. For other sites, positive associations were observed only for specific metabolic factors, that is, high triglycerides and male colon cancer (HR=1.71, CI=1.11–2.62), and obesity and female breast cancer (HR=1.75, CI=1.21–2.55). Metabolic factors in the aggregate may have little impact on total cancer risk in the Japanese population, although the association between specific components and specific cancers suggests an etiologic link between them. *European Journal of Cancer Prevention* **18:240–247 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, [b]Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, Tokyo and [c]Public Health, Department of Social and Environmental Medicine, Osaka University Graduate School of Medicine, Osaka, Japan

Correspondence to Dr Manami Inoue, MD, PhD, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel: +81 3 3542 2511 x3389; fax: +81 3 3547 8578;
e-mail: mnminoue@ncc.go.jp

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Introduction

Metabolic syndrome has become recognized as a major public health target worldwide, associated with the global pandemic of obesity and diabetes (Alberti *et al.*, 2005; Eckel *et al.*, 2005). The constellation of factors in metabolic syndrome, namely glucose intolerance and insulin resistance, central obesity, dyslipidemia, and hypertension, are also well-documented risk factors for cardiovascular disease and diabetes (Eckel *et al.*, 2005; Zambon *et al.*, 2005). As most of these components have suggestive links to the development of cancer, the possible association of metabolic factors in the aggregate with cancer risk has been speculated (Hamet, 1997; Mason, 1999; Yu and Rohan, 2000; Calle and Thun, 2004; Cowey and Hardy, 2006; Barb *et al.*, 2007; Giovannucci, 2007; Hsing *et al.*, 2007; Hsu *et al.*, 2007; Watanabe *et al.*, 2007; Xue and Michels, 2007). Epidemiologic evidence for this link is, however, limited (Russo *et al.*, 2008), and most has been targeted at specific sites of cancer (Trevisan *et al.*, 2001; Colangelo *et al.*, 2002; Furberg *et al.*, 2004; Laukkanen *et al.*, 2004; Ahmed *et al.*, 2006; Bowers *et al.*, 2006; Lund Haheim *et al.*, 2006; Sturmer *et al.*, 2006; Tande *et al.*, 2006; Beebe-Dimmer *et al.*, 2007; Chiu *et al.*, 2007; Cust *et al.*, 2007; Tuohimaa *et al.*, 2007). To date, no conclusive evidence has been obtained.

As in many countries, metabolic syndrome has recently attracted substantial attention in Japan, reflected in the decision of the government to start a nationwide intervention strategy beginning April 2008. The National Health and Nutrition Survey in Japan reported that the prevalence of metabolic syndrome in the Japanese

Study group members are listed in the appendix

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population in 2005, by the modified definition of the International Diabetes Federation (IDF) (Alberti *et al.*, 2006), that is, the presence of central obesity and any two of three additional factors [hypertension, hyperglycemia defined by HbA1c and low high-density lipoprotein (HDL)-cholesterol], was 25.5% in men and 10.3% in women aged 40–74 years (Ministry of Health, Labour and Welfare, 2007). Given the expectation that this would likely influence related health conditions, including cancer, clarification of the association between metabolic factors and cancer is a crucial task, not only from a causative point of view, but also with regard to the formulation of clinical and public health strategies for the target population.

Here, we conducted a cohort analysis on the association between metabolic factors and cancer risk using a large-scale population-based study in Japan. Our main purpose was to clarify whether metabolic factors, either individually or in the aggregate, predict the subsequent occurrence of total and major sites of cancer in the Japanese population.

Methods

Study population

The Japan Public Health Center-Based Prospective Study was conducted in two cohorts, one initiated in 1990 (cohort I) and the other in 1993–1994 (cohort II), which targeted all registered Japanese inhabitants in 11 public health center (PHC) areas aged 40–59 years in cohort I and 40–69 years in cohort II at the beginning of each baseline survey. Details of the study design have been provided elsewhere (Tsugane and Sobue, 2001). The study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan (approval no. 13–21). In this analysis, one PHC area was excluded, as data on cancer incidence were not available.

Data on metabolic factors, that is, serum HDL-cholesterol, serum triglycerides, glucose, blood pressure, height, and weight, were available for 30 170 participants aged 40–69 years who responded to the self-administered questionnaire and undertook health examinations conducted by municipal governments in 1995 (cohort I) and 1993–1994 (cohort II). We excluded participants who reported a diagnosis of cancer before the start point (n=612) or who had missing data for items included in the multivariate analysis (n=1834), leaving 27 724 participants (9548 men and 18 176 women) for analysis.

Follow-up

Participants were followed from the date of the baseline survey until 31 December 2004. Residence status, including survival, was confirmed through the residential registry. Inspection of the registry is available to anyone under the resident registration law. Among the study participants, 710 died, 1520 moved out of the study area, and 34 (0.1%) were lost to follow-up within the follow-up period. Information on the cause of death was obtained from the death certificate, provided by the Ministry of Health, Labour, and Welfare with the permission of the Ministry of Internal Affairs and Communications, in which cause of death is defined according to the International Classification of Disease, 10th version (World Health Organization, 1990). Resident and death registration are required by law in Japan, and the registries are believed to be complete.

Measurements

Serum total and HDL-cholesterol, triglycerides, and glucose were measured in 23 laboratories. Precision and accuracy in all laboratories was found to be satisfactory according to the Osaka Medical Center for Health Science and Promotion (Iida *et al.*, 2001), a member of the Cholesterol Reference Method Laboratory Network (Nakamura *et al.*, 2003). Trained technicians measured blood pressure using standard mercury sphygmomanometers. Height was measured in stocking feet and weight in light clothing. Body mass index (BMI) was calculated from the height and weight by using the formula weight (kg)/height^2(m^2). Smoking and alcohol consumption status were ascertained by the questionnaire.

Participants were categorized by the number of metabolic factors, similarly to the definitions of the American Heart Association/National Heart, Lung, and Blood Institute (Grundy *et al.*, 2005) and IDF (Alberti *et al.*, 2006). Being overweight with a BMI $\geq 25.0\,kg/m^2$ was used as the criterion for obesity, as this BMI level was reported to correspond well to the Japanese criteria for a large waist circumference of $\geq 85\,cm$ in men and $\geq 90\,cm$ in women, and $100\,cm^2$ of visceral fat area (Examination Committee of Criteria for 'Obesity Disease' in Japan: Japan Society for the Study of Obesity, 2002), and as waist circumference was not measured in this study. The metabolic factors were defined as follows: (i) high blood pressure: blood pressure $\geq$ 130/85 mmHg and/or medication use; (ii) high glucose: glucose $\geq$ 5.55 mmol/l (100 mg/dl) fasting or $\geq$ 7.77 mmol/l (140 mg/dl) non-fasting, and/or on treatment; (iii) low HDL-cholesterol less than 1.03 mmol/l (40 mg/dl) for men and less than 1.29 mmol/l (50 mg/dl) for women; (iv) high triglycerides: high serum triglycerides $\geq$ 1.69 mmol/l (150 mg/dl); and (v) being overweight: BMI $\geq 25\,kg/m^2$. As a key difference among current criteria for metabolic syndrome is whether obesity should be included as an essential prerequisite, metabolic aggregate in this study was defined as the presence of three or more of the following factors: three or more than three factors (high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and being overweight), similar to the criteria of the American Heart Association/National Heart, Lung, and Blood Institute, as well as the presence of two or more of the additional components (high blood pressure, high glucose, low HDL-cholesterol, and

high triglycerides) among overweight persons: two or more than two additional factors in addition to being overweight, similar to the criteria of the IDF.

Ascertainment of cancer incidence

The occurrence of cancer was identified by voluntary notification from the major hospitals in the study area and data linkage with population-based cancer registries. Death certificates were used as a supplementary information source. The site and histology of each case were coded using the International Classification of Diseases for Oncology, third edition (World Health Organization, 2000). In this dataset, the proportion of cases for which information was available from death certificates only was 4.3%. For the present analysis, the earliest date of diagnosis was used in participants with multiple primary cancers at different times. A total of 1858 newly diagnosed cancer cases were identified.

Analysis

The number of person-years in the follow-up period was counted from the date of baseline survey until the date of occurrence of any cancer, date of emigration from the study area, date of death, or end of the study period, whichever came first. For participants who withdrew from or were lost to follow-up, the date of withdrawal and the last confirmed date of presence, respectively, were used as the date of censor.

The relative risk of cancer occurrence associated with each metabolic factor and with the two criteria for metabolic aggregate was described using hazard ratios (HR) and 95% confidence intervals (CI). The Cox proportional hazards model was used to control for potential confounding factors, such as age at baseline, study area (10 PHC areas), smoking status (never, past, < 20 cigarettes per day, 20–29 cigarettes per day, ≥ 30 cigarettes per day), weekly ethanol intake (< weekly, < 150 g per week, 150– < 300 g per week, ≥ 300 g per week), daily total physical activity level (quartile of metabolic equivalents) and total cholesterol (mg/dl, continuous). These variables, obtained from the questionnaire, are either known or suspected from earlier studies to be risk factors for cancer. Age and area were treated as strata to allow for a different baseline hazard for each stratum. Testing of the proportional hazards assumption by Schoenfeld and scaled Schoenfeld residuals found no violation of proportionality. All statistical analyses were performed using Stata 10 (Stata Corporation, College Station, Texas, USA) (Stata Corporation, 2007).

Results

During 283 493 person-years of follow-up (average follow-up period: 10.2 years) for 27 724 participants (9548 men and 18 176 women), a total of 1858 cases of newly diagnosed cancer (986 men and 872 women) were identified and included in the analyses.

According to the definitions of the respective metabolic factors, 60% of study participants had high blood pressure, 23% had high glucose, 16% had low HDL-cholesterol, 31% had high triglycerides, and 30% were overweight among men. In addition, 52% had high blood pressure, 12% had high glucose, 28% had low HDL-cholesterol, 21% had high triglycerides, and 30% were overweight among women. As a consequence, 23% of men and 19% of women were categorized as having three or more than three metabolic factors, and 17% of men and 14% of women as having two or more than two factors, in addition to being overweight (Table 1).

The HRs (CI) of all sites and major sites of cancer according to the presence of metabolic factors are shown in Tables 2 (for men) and 3 (for women). Neither the presence of metabolic syndrome nor that of any metabolic factor was associated with increased risk of total cancer in either sex.

In contrast, risk varied by site of cancer. In men, the presence of metabolic factors in the aggregate was associated with an increased risk of liver cancer [HR=1.73, CI=1.03–2.91 (three or more than three factors); HR=1.99, CI=1.11–3.58 (two or more than two additional factors in addition to being overweight)]. Liver cancer was also associated with metabolic factors, namely high glucose (HR=1.76, CI=1.07–2.89), low HDL-cholesterol (HR=2.25, CI=1.34–3.79), and being overweight (HR=2.18, CI=1.33–3.58). High triglycer-

Table 1 Baseline characteristics of study participants ($n=27\,724$)

	Men	Women
Number of participants	9548	18 176
Total person-years	94 972	188 521
Age [mean (year ± SD)]	56.5 ± 8.2	55.5 ± 8.1
Smoking status (%)		
Never	29.9	94.6
Past	27.6	1.3
< 20 Cigarettes per day	12.2	2.9
20–29 Cigarettes per day	19.0	1.0
≥ 30 Cigarettes per day	11.3	0.2
Weekly ethanol intake (%)		
Less than weekly	24.8	82.2
< 150 g per week	30.8	16.0
150– < 300 g per week	21.6	1.3
≥ 300 g per week	22.8	0.5
Daily total physical activity level (median METs)		
Lowest quartile	26.10	26.50
Second quartile	31.85	31.85
Third quartile	42.65	34.25
Highest quartile	45.05	42.65
Serum total cholesterol (mg/dl) (mean ± SD)	196.5 ± 34.2	209.3 ± 34.6
Metabolic factor (%)		
High blood pressure	60.0	51.7
High glucose	22.6	11.9
Low HDL-cholesterol	16.1	28.1
High triglycerides	30.5	20.6
Overweight	29.8	30.4
≥ 3 Factors	22.5	19.1
≥ 2 Factors in addition to being overweight	16.8	14.2

HDL, high-density lipoprotein; MET, metabolic equivalent.

Table 2 Hazard ratios[a] (95% confidence interval) of cancer according to metabolic factors in men ($n=9548$)

	Metabolic factors in the aggregate		Components of metabolic factors				
	≥ 3 Factors	≥ 2 Factors in addition to being overweight	High blood pressure	High glucose	Low HDL-cholesterol	High triglycerides	Overweight
Number of participants	2146	1603	5733	2161	5109	2915	2847
Person-years	21 671	16 279	57 084	21 687	15 027	29 124	28 749
All sites ($n=986$)							
Number of cases	197	142	665	233	167	245	269
HR (95% CI)	0.90 (0.77–1.05)	0.92 (0.77–1.11)	1.04 (0.90–1.19)	1.01 (0.87–1.17)	1.13 (0.95–1.35)	0.89 (0.76–1.03)	1.02 (0.88–1.18)
Stomach ($n=233$)							
Number of cases	44	29	156	59	41	50	49
HR (95% CI)	0.87 (0.62–1.21)	0.85 (0.57–1.26)	1.01 (0.76–1.34)	1.06 (0.78–1.43)	1.20 (0.85–1.71)	0.73 (0.53–1.02)	0.78 (0.56–1.08)
Colon ($n=102$)							
Number of cases	27	19	69	22	15	40	24
HR (95% CI)	1.29 (0.82–2.02)	1.24 (0.75–2.07)	0.99 (0.64–1.52)	0.83 (0.51–1.34)	1.15 (0.65–2.03)	1.71 (1.11–2.62)	0.80 (0.50–1.28)
Rectum ($n=53$)							
Number of cases	8	8	36	10	4	10	19
HR (95% CI)	0.62 (0.29–1.34)	0.94 (0.44–2.05)	1.18 (0.65–2.15)	0.81 (0.40–1.64)	0.41 (0.14–1.16)	0.54 (0.26–1.11)	1.53 (0.85–2.75)
Liver ($n=74$)							
Number of cases	21	15	55	26	25	15	27
HR (95% CI)	1.73 (1.03–2.91)	1.99 (1.11–3.58)	1.60 (0.93–2.75)	1.76 (1.07–2.89)	2.25 (1.34–3.79)	0.98 (0.54–1.78)	2.18 (1.33–3.58)
Pancreas ($n=24$)							
Number of cases	2	2	12	4	3	6	3
HR (95% CI)	0.28 (0.07–1.22)	0.42 (0.10–1.81)	0.61 (0.26–1.41)	0.74 (0.24–2.22)	0.59 (0.17–2.06)	0.62 (0.23–1.63)	0.33 (0.10–1.12)
Lung ($n=149$)							
Number of cases	30	23	103	31	29	38	41
HR (95% CI)	0.86 (0.57–1.30)	0.99 (0.63–1.56)	1.17 (0.81–1.68)	0.85 (0.57–1.27)	1.03 (0.68–1.58)	0.93 (0.63–1.38)	1.10 (0.76–1.60)
Prostate ($n=119$)							
Number of cases	22	14	86	27	15	30	35
HR (95% CI)	0.76 (0.47–1.22)	0.65 (0.37–1.15)	1.21 (0.80–1.83)	1.01 (0.65–1.58)	0.99 (0.57–1.73)	0.82 (0.53–1.27)	0.99 (0.66–1.48)

CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratios.
[a]Adjusted for age (stratified, 5-year age categories), study area (stratified, 10 public health center areas), smoking status (never, past, <20 cigarettes per day, 20–29 cigarettes per day, ≥ 30 cigarettes per day), weekly ethanol intake (<weekly, <150 g per week, 150–<300 g per week, ≥ 300 g per week), and total serum cholesterol (mg/dl, continuous).

Table 3 Hazard ratios[a] (95% confidence interval) of cancer according to the metabolic factors in women ($n=18\,176$)

	Metabolic factors in the aggregate		Components of metabolic factors				
	≥ 3 Factors	≥ 2 Factors in addition to being overweight	High blood pressure	High glucose	Low HDL-cholesterol	High triglycerides	Overweight
Number of participants	3476	2576	9388	2166	1539	3737	5521
Person-years	36 402	26 953	98 333	22 683	53 113	38 904	57 777
All sites ($n=872$)							
Number of cases	183	145	480	114	253	191	293
HR (95% CI)	0.99 (0.84–1.17)	1.10 (0.92–1.32)	0.91 (0.79–1.05)	1.07 (0.87–1.31)	0.99 (0.85–1.14)	0.99 (0.84–1.17)	1.08 (0.94–1.25)
Stomach ($n=138$)							
Number of cases	24	17	77	21	40	31	37
HR (95% CI)	0.77 (0.49–1.21)	0.80 (0.48–1.34)	0.83 (0.58–1.18)	1.14 (0.71–1.84)	0.94 (0.65–1.37)	1.06 (0.70–1.62)	0.85 (0.58–1.25)
Colon ($n=106$)							
Number of cases	24	19	66	13	32	25	36
HR (95% CI)	1.03 (0.65–1.65)	1.14 (0.69–1.89)	1.07 (0.71–1.62)	0.90 (0.50–1.64)	1.12 (0.74–1.71)	1.00 (0.63–1.60)	1.04 (0.69–1.57)
Rectum ($n=51$)							
Number of cases	12	10	25	8	17	8	16
HR (95% CI)	0.99 (0.51–1.92)	1.17 (0.58–2.35)	0.60 (0.34–1.06)	1.35 (0.62–2.92)	1.14 (0.63–2.06)	0.52 (0.24–1.13)	0.92 (0.50–1.68)
Liver ($n=40$)							
Number of cases	9	8	20	6	12	4	18
HR (95% CI)	1.18 (0.55–2.51)	1.50 (0.68–3.31)	0.68 (0.35–1.30)	1.18 (0.49–2.86)	0.84 (0.42–1.69)	0.58 (0.20–1.68)	1.95 (1.03–3.69)
Pancreas ($n=41$)							
Number of cases	15	12	26	6	17	12	15
HR (95% CI)	1.80 (0.94–3.45)	1.99 (1.00–3.96)	1.05 (0.54–2.03)	1.00 (0.42–2.39)	1.52 (0.81–2.86)	1.23 (0.61–2.49)	1.16 (0.61–2.22)
Lung ($n=75$)							
Number of cases	12	8	39	9	20	18	19
HR (95% CI)	0.66 (0.35–1.24)	0.61 (0.29–1.29)	0.75 (0.47–1.21)	1.00 (0.49–2.03)	0.89 (0.53–1.49)	0.98 (0.57–1.70)	0.71 (0.42–1.20)
Breast ($n=120$)							
Number of cases	19	18	59	12	25	24	51
HR (95% CI)	0.82 (0.50–1.36)	1.12 (0.67–1.87)	0.96 (0.66–1.41)	0.90 (0.49–1.67)	0.65 (0.41–1.02)	0.97 (0.61–1.55)	1.75 (1.21–2.55)

CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratios.
[a]Adjusted for age (stratified, 5-year age categories), study area (stratified, 10 public health center areas), smoking status (never, past, <20 cigarettes per day, 20–29 cigarettes per day, ≥ 30 cigarettes per day), weekly ethanol intake (<weekly, <150 g per week, 150–<300 g per week, ≥ 300 g per week), and total serum cholesterol (mg/dl, continuous).

ides were associated with an increased risk of colon cancer (HR=1.71, CI=1.11–2.62). No notable association was found between the presence of metabolic factors and other cancers.

In women, the presence of metabolic factors was associated only with the risk of pancreatic cancer [HR=1.99, CI=1.00–3.96 (two or more than two additional factors in addition to being overweight)]. By component, being overweight significantly increased the risk of liver (HR=1.95, CI=1.03–3.96) and breast cancer (HR=1.75, CI=1.21–2.55).

Discussion

Metabolic syndrome has been fundamentally recognized as a cardiovascular risk factor because of its components such as hypertension, insulin resistance, dyslipidemia, and obesity. As insulin resistance and obesity are often suggested to have a link with cancer (Yu and Rohan, 2000; Calle and Thun, 2004; Cowey and Hardy, 2006; Barb *et al.*, 2007; Hsu *et al.*, 2007), an association between metabolic syndrome and cancer is also suspected. Earlier studies on this association have mainly focused on specific sites of cancer, including colon, prostate, breast, and endometrial cancer (Trevisan *et al.*, 2001; Colangelo *et al.*, 2002; Furberg *et al.*, 2004; Laukkanen *et al.*, 2004; Ahmed *et al.*, 2006; Bowers *et al.*, 2006; Lund Haheim *et al.*, 2006; Sturmer *et al.*, 2006; Tande *et al.*, 2006; Beebe-Dimmer *et al.*, 2007; Chiu *et al.*, 2007; Cust *et al.*, 2007; Tuohimaa *et al.*, 2007; Russo *et al.*, 2008), which are common in Western populations (Ferlay *et al.*, 2004) and are considered to have an etiologic link with these components (Cowey and Hardy, 2006; Giovannucci, 2007; Hsing *et al.*, 2007; Hsu *et al.*, 2007; Xue and Michels, 2007). To what extent the grand sum of the effect on these sites of cancer affects total cancer incidence has, however, not been clarified. In our prospective cohort study, the presence of metabolic factors in the aggregate did not predict subsequent occurrence of cancer as a whole. By site, a significant increase in risk was observed only for liver cancer in men and pancreatic cancer in women. It appears from our results that the components of metabolic factors better predict the occurrence of cancer, as opposed to metabolic abnormality in the aggregate.

Earlier studies focusing on the impact of metabolic factors in the aggregate on total cancer risk are sparse. The only study, from Italy, recently reported null association for total cancer incidence (Russo *et al.*, 2008), which accords with our result.

By site, our results showed a significantly increased risk of liver cancer in men with the presence of metabolic factors in the aggregate, an association also observed for its components, including high glucose, low HDL-cholesterol, and being overweight. With metabolic abnormality, free fatty acids are released in abundance from an expanded adipose tissue mass. In the liver, free fatty acids produce an increased production of glucose, triglycerides, and secretion of very low-density lipoproteins, with lipid/lipoprotein abnormalities such as reductions in HDL-cholesterol and an increased density of low-density lipoproteins (Alberti *et al.*, 2005). In addition, a significant proportion (7–30%) of cases of hepatocellular carcinoma develops in cryptogenic cirrhosis, which may actually represent nonalcoholic fatty liver steatohepatitis (Bugianesi, 2005). It is known that nonalcohol fatty liver disease, including nonalcoholic fatty liver steatohepatitis, is tightly associated with insulin resistance and several features of metabolic abnormality (Bugianesi *et al.*, 2004), and this in turn suggests a link between metabolic factors and liver cancer. The strongest risk factor for liver cancer is, however, hepatitis virus infection, whose role in the association between metabolic factors and cancer has not been well clarified. Our study did not consider hepatitis virus infection, and this question should be solved in future studies.

We also observed an increased risk of pancreatic cancer with metabolic factors in women. Evidence of this association is also sparse, with the only study reported to date showing an increased risk in men but not in women (World Cancer Research Fund/American Institute for Cancer Research, 2007). We cannot deny the possibility that ours was a chance finding because of the small number of cases. Nevertheless, an association is likely, as insulin resistance, or in other words a decrease in the normal response of pancreatic β cells to insulin, may explain many of the factors associated with metabolic abnormality (Cowey and Hardy, 2006), although the sex difference in the results remains to be clarified.

For other sites of cancer, we observed a positive association with specific metabolic components only site specifically, that is, high triglycerides and colon cancer in men and overweight and breast cancer in women. Earlier studies on the positive association between triglycerides and colon cancer have been inconsistent (Giovannucci, 2007). Obesity convincingly increases the risk of postmenopausal breast cancer (World Cancer Research Fund/American Institute for Cancer Research, 2007). Although menopausal status was not considered in this analysis, our earlier report focusing on this association noted an increased risk in postmenopausal women only (Iwasaki *et al.*, 2007).

Although we are unable to disregard the role of metabolic factors in the association with cancer, a number of them are suggested to be related to one another; in other words, the metabolic factors promote cancer through various mechanisms that then act in an additive or synergistic manner (Cowey and Hardy, 2006). Specifically, these components may promote cancer development by generating reactive oxygen species; by increasing hormone production/bioavailability, including that of estrogen,

insulin-like growth factor-1, insulin, and adipokines; and by providing an energy-rich environment. Together, this imbalance of hormones, the redox system and energy availability promote cell transformation, angiogenesis, migration, and proliferation, as well as the inhibition of apoptosis. These mechanisms have, in turn, been linked to obesity, insulin resistance, glucose, and triglycerides/fatty acids. However, the potential molecular mechanisms linking HDL-cholesterol and hypertension to cancer remain unclear (Cowey and Hardy, 2006). An earlier study on breast cancer suggested that HDL-cholesterol is not a risk factor *per se*, but rather a marker for several variables, including reproductive history and other risk factors, involved in the etiology of the cancer (Ferraroni *et al.*, 1993).

Against these potential mechanisms, the impact of metabolic factors in the aggregate did not seem to be substantial in our population. This may be because of background characteristics of this population, namely the proportion of individual metabolic components, which are strongly or weakly associated with cancer, and the site distribution of cancers, which are strongly or weakly associated with metabolic factors. Hypertension is known to be a major contributing risk factor for cardiovascular disease, but not for cancer. In our population, the prevalence of hypertension was relatively high compared with that of other factors, a finding consistent with the results of a recent national survey in Japan (Ministry of Health, Labour and Welfare, 2007). In addition, the incidence of cancers associated with obesity, hyperglycemia, and dyslipidemia such as colon, prostate, breast, and endometrial cancer in our population was low compared with Western populations (Ferlay *et al.*, 2004), in whom the prevalence of these factors is higher than in the Japanese population (Ford *et al.*, 2002; Hu *et al.*, 2004). On these bases, the contribution of metabolic factors in the aggregate on the risk of cancer may not have been as large as in other populations, where obesity and insulin resistance predominate.

The major strength of this study is its prospective design, in which information was collected before the subsequent diagnosis of cancer, thereby avoiding the exposure recall bias inherent to case–control studies. Other strengths include the fact that the study participants were selected from the general population, that the proportion of loss to follow-up (0.1%) was negligible, that the quality of our cancer registry system was satisfactory over the study period, and that potential confounding factors could be adjusted to minimize their influence on risk values, in spite of the possible influence of residual confounding.

Against this, several obvious limitations can be identified. First, waist circumference was not available to assess exposure. Previous studies, however, reported that a BMI of 25.0 kg/m^2 was equal to 100 cm^2 of visceral fat area as central obesity (Examination Committee of Criteria for 'Obesity Disease' in Japan: Japan Society for the Study of Obesity, 2002), and thus misclassification by the use of BMI instead of waist circumference, if any, might be small. Likewise, we used nonfasting data, in particular nonfasting triglycerides $\geq$ 1.69 mmol/l (150 mg/dl), as a metabolic component, although justification for the use of the same cut-off point as for fasting status is presently under debate. In this study, analyses limited to fasting participants yielded closely similar results. Second, evaluation by single measurement of metabolic factors at baseline might have produced misclassification, although this would likely be nondifferential and lead to an underestimation of results. Moreover, the duration of exposure to these metabolic factors is likely longer in established Western populations than in the Japanese population, which has become more westernized in lifestyle over a relatively few recent years.

Further, the subjects of this study were restricted to 21% of the total study participants, who provided complete information in their response to the questionnaire and health checkup data. More women than men tend to participate in health checkup surveys provided by local governments. In addition, participants often differ from nonparticipants in socioeconomic status, and women in particular have a more favorable lifestyle profile, including lower smoking rates, greater participation in physical exercise, and higher intake of green vegetables and fruits (Iwasaki *et al.*, 2003, 2006). Differences in these factors may have influenced the association between metabolic factors and cancer. In addition, total cancer incidence in this study population during the follow-up period was 655 per 100 000 person-years, versus 713 in the whole Japan Public Health Center-based Prospective Study, suggesting that participants who were already under care for any of the metabolic factors may have been less willing to attend a health checkup, which in turn may have led to the underestimation of risk. Together, these considerations mandate the need for caution in interpreting or generalizing these results.

Allowing for these methodological issues, our results suggest that metabolic factors in the aggregate have little impact on the subsequent risk of total cancer in the Japanese population. Liver cancer, which has a significant link with the presence of metabolic factors, requires further study to determine the influence of hepatitis infection on this association. The association between specific metabolic factors and specific cancers observed in our study suggests the presence of an etiologic link between them.

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Appendix

Members of the Japan Public Health Center-based Prospective Study (JPHC Study, principal investigator: S. Tsugane) Group are as follows:

S. Tsugane, M. Inoue, T. Sobue, and T. Hanaoka, National Cancer Center, Tokyo; J. Ogata, S. Baba, T.

Mannami, A. Okayama, and Y. Kokubo, National Cardiovascular Center, Osaka; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, T. Ikuta, and Y. Tanaba, Iwate Prefectural Ninohe Public Health Center, Iwate; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, and N. Nagai, Akita Prefectural Yokote Public Health Center, Akita; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Y. Miyagawa, and Y. Kobayashi, Nagano Prefectural Saku Public Health Center, Nagano; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei, and H. Sakiyama, Okinawa Prefectural Chubu Public Health Center, Okinawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, F. Shoji, and R. Saito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, and T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Ibaraki; K. Matsui, T. Abe, M. Katagiri, and M. Suzuki, Niigata Prefectural Kashiwazaki and Nagaoka Public Health Center, Niigata; M. Doi, A. Terao, Y. Ishikawa, and T. Tagami, Kochi Prefectural Chuo-higashi Public Health Center, Kochi; H. Sueta, H. Doi, M. Urata, N. Okamoto, and F. Ide, Nagasaki Prefectural Kamigoto Public Health Center, Nagasaki; H. Sakiyama, N. Onga, H. Takaesu, and M. Uehara, Okinawa Prefectural Miyako Public Health Center, Okinawa; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, and M. Takano, Osaka Prefectural Suita Public Health Center, Osaka; Y. Tsubono, Tohoku University, Miyagi; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Honda, K. Yamagishi, S. Sakurai, and N. Tsuchiya, Tsukuba University, Ibaraki; M. Kabuto, National Institute for Environmental Studies, Ibaraki; M. Yamaguchi, Y. Matsumura, S. Sasaki, and S. Watanabe, National Institute of Health and Nutrition, Tokyo; M. Akabane, Tokyo University of Agriculture, Tokyo; T. Kadowaki, Tokyo University, Tokyo; M. Noda and T. Mizoue, International Medical Center of Japan, Tokyo; Y. Kawaguchi, Tokyo Medical and Dental University, Tokyo; Y. Takashima and M. Yoshida, Kyorin University, Tokyo; K. Nakamura, Niigata University, Niigata; S. Matsushima and S. Natsukawa, Saku General Hospital, Nagano; H. Shimizu, Sakihae Institute, Gifu; H. Sugimura, Hamamatsu University, Shizuoka; S. Tominaga, Aichi Cancer Center Research Institute, Aichi; H. Iso, Osaka University, Osaka; M. Iida, W. Ajiki, and A. Ioka, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Chiba Prefectural Institute of Public Heath, Chiba; E. Maruyama, Kobe University, Hyogo; M. Konishi, K. Okada, and I. Saito, Ehime University, Ehime; N. Yasuda, Kochi University, Kochi; S. Kono, Kyushu University, Fukuoka.

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ORIGINAL PAPER

Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II)

Manami Inoue · Norie Kurahashi · Motoki Iwasaki · Yasuhito Tanaka · Masashi Mizokami · Mitsuhiko Noda · Shoichiro Tsugane · for the Japan Public Health Center-based Prospective Study Group

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Abstract
Objective The association between metabolic factors and hepatocellular carcinoma (HCC) has not been well clarified. We prospectively examined whether metabolic factors predicts the subsequent risk of HCC in the Japan Public Health Center-based Prospective Study Cohort II, in consideration of hepatitis virus infection status.
Methods A total of 17,590 subjects aged 40–69 participating in a questionnaire and health checkup survey during 1993–1994 were followed for incidence of HCC through 2006. A total of 102 cases of HCC were newly documented. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for metabolic factors controlling for potential confounding factors.
Results The presence of metabolic factors in the aggregate was associated with a significantly increased risk of HCC, especially with hepatitis virus infection. HCC was positively associated particularly with high glucose (HR = 1.75, CI = 1.11–2.74) and overweight (HR = 2.22, CI = 1.42–3.48). Results were similar when analyses were limited to subjects with HCV infection.
Conclusions Although metabolic factors in the aggregate may be associated with an increased risk of HCC, the main contributors to this association under HCV infection appear to be overweight and high glucose. Improvement of these factors may be a crucial target in preventing progression to HCC in those with HCV infection.

Keywords Metabolic factor · Hepatocellular carcinoma · Cohort study · Overweight · High glucose

Introduction

Although a link with hepatocellular carcinoma (HCC) has been suggested for some of its individual components, a role for metabolic factors overall as a risk factor for the development of HCC remains unproven [1]. It is known that a significant proportion of cases of HCC develops in cryptogenic cirrhosis, which may actually represent non-alcoholic fatty liver steatohepatitis (NASH) [2]. Non-alcohol fatty liver disease (NAFLD), a category which includes NASH, is closely associated with insulin resistance and several features of metabolic factors [3], in turn, suggesting a link between metabolic factors and HCC. Meanwhile, hepatitis C virus (HCV) is linked with impaired insulin resistance and diabetes, hypocholesterolemia, and steatosis, which together represent a distinct HCV-associated dysmetabolic change [1]. Diabetes is also acknowledged as an independent risk factor for the development of HCC [4], strongly suggesting that HCV

The members of the Japan Public Health Center-based Prospective Study Group are listed in Appendix.

M. Inoue (✉) · N. Kurahashi · M. Iwasaki · S. Tsugane
Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: mnminoue@ncc.go.jp

Y. Tanaka · M. Mizokami
Department of Clinical Molecular Informative Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

M. Noda
Department of Diabetes and Metabolic Medicine, International Medical Center of Japan, Tokyo, Japan

for the Japan Public Health Center-based Prospective Study Group
Tokyo, Japan

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infection may be a promoter of the development of HCC by way of insulin-mediated pathways.

The primary causes of HCC, which remains one of the most important cancers in Japan [5, 6], are HCV and hepatitis B virus (HBV) infection [7]. Meanwhile, metabolic factors have become recognized as a major public health target worldwide, and associated with the global pandemic of obesity and diabetes [8]. Given the expectation that metabolic factors influence the incidence of HCC, clarification of the association between metabolic factors and HCC is a crucial task. However, epidemiological evidence for this link is limited [9, 10], and most previous epidemiological studies have targeted individual components of metabolic factors, such as diabetes [4, 10–21] and obesity [10, 21–26]. Further, only a few of these studies have taken account of hepatitis virus infection status [10, 13, 15–20].

Here, we conducted a cohort analysis on the association between metabolic factors and risk of HCC using a large-scale population-based study in Japan. Our main purpose was to clarify whether metabolic factors predict the subsequent occurrence of HCC in Japanese, and whether the effect is attributable to specific components or to an aggregate effect, in consideration of hepatitis virus infection status.

Methods

The Japan Public Health Center-based Prospective Study (JPHC Study) Cohort II was initiated in 1993–1994. This cohort consisted of six public health center (PHC) areas across Japan. The study design had been described in detail previously [27]. The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. The study population was defined as all residents aged 40–69 years at the start of the baseline survey. A part of one PHC area was excluded because its study population was defined differently to the others. Initially, we defined a population-based cohort of 68,975 subjects after exclusion of ineligible subjects ($n = 103$).

Baseline survey

At baseline, a self-administered questionnaire survey on various lifestyle factors was conducted (response rate = 82%). A total of 10 ml of blood was also arranged voluntarily by 39% of the respondents during health checkups provided by the local government. The plasma and buffy layer were divided into four tubes holding 1.0 ml each (three tubes for plasma and one for the buffy layer) and stored at −80°C until analysis.

For this research analysis, we restricted subjects to those who responded to the questionnaire and for whom blood samples and health checkup data on components of metabolic factors were available, i.e., blood pressure, blood glucose, serum HDL-cholesterol, serum triglycerides, height, and weight. We further excluded those with a history of liver cancer and those with missing data on variables to be controlled such as smoking status, weekly ethanol intake, coffee intake, and serum total cholesterol. Finally, a total of 17,590 individuals were included in this analysis.

Measurements

Serum total and HDL-cholesterol, triglycerides, and glucose were measured in 23 laboratories. Precision and accuracy in all the laboratories were found to be satisfactory according to the Osaka Medical Center for Health Science and Promotion [28], a member of the Cholesterol Reference Method Laboratory Network (CRMLN) [29]. Trained technicians measured blood pressure using standard mercury sphygmomanometers. Height was measured in stocking feet and weight in light clothing. Body mass index (BMI) was calculated from the height and weight using the formula weight (kg)/height $(m)^2$.

Subjects were categorized by the number of metabolic factors, according to the definitions of the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) [30] and International Diabetes Federation (IDF) [31]. Waist circumference was not measured in this study. Overweight with a BMI $\geq$ 25.0 kg/m^2 was used as the criterion for central obesity, because this BMI level was reported to correspond well to the Japanese criteria for a high waist circumference of $\geq$85 cm in men and $\geq$90 cm in women, and 100 cm^2 of visceral fat area [32]. The metabolic factors were defined as follows: (1) high blood pressure: blood pressure $\geq$130/85 mmHg and/or medication use; (2) high glucose: blood glucose $\geq$5.55 mmol/l (100 mg/dl) fasting or $\geq$7.77 mmol/l (140 mg/dl) non-fasting, and/or on treatment; (3) low HDL-cholesterol <1.03 mmol/l (40 mg/dl) for men and <1.29 mmol/l (50 mg/dl) for women; (4) high triglycerides: high serum triglycerides $\geq$1.69 mmol/l (150 mg/dl); (5) overweight: BMI $\geq$ 25 kg/m^2. Metabolic aggregate in this study was defined as the presence of three or more of these components (high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and overweight), similar to the criteria of the AHA/NHLBI; and the presence of two or more of the additional components (high blood pressure, high glucose, low HDL-cholesterol, and high triglycerides) among overweight persons, similar to the criteria of the IDF.

Laboratory assays

Plasma samples were screened for anti-HCV antibody (anti-HCV) using a third-generation immunoassay (Lumipulse II

Ortho HCV, Ortho-Clinical Diagnosis K.K., Tokyo, Japan) [33] and for hepatitis B virus antigen (HBsAg) by reversed passive hemagglutination with a commercial kit (Institute of Immunology Co., Ltd., Tokyo, Japan).

Follow-up and identification of HCC

Subjects were followed from the date of the baseline survey until 31 December 2006. Residence status, including survival, was confirmed through the residential registry. Inspection of the registry is available to anyone under the resident registration law. Information on the cause of death was obtained from the death certificate, provided by the Ministry of Health, Labour, and Welfare with the permission of the Ministry of Internal Affairs and Communications, in which cause of death is defined according to the International Classification of Disease, 10th Version (ICD-10) [34]. Resident and death registration are required by law in Japan and the registries are believed to be complete. Among study subjects, 1,578 died, 961 moved out of the study area, and 47 (0.3%) were lost to follow-up within the follow-up period.

The incidence data on HCC were obtained by active patient notification from major hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Death certificates were used as a supplementary information source. In our cancer registry system, the proportion of cases for which information was available from death certificates only was 4.7%. The site and histology of each HCC case were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3: C22.0) [35]. For this analysis, the earliest date of diagnosis was used in subjects with multiple primary cancers at different times. A total of 102 newly diagnosed cancer cases (67 for men, 35 for women) were identified.

Analysis

The number of person-years in the follow-up period was counted from the date of completion of the baseline questionnaire until the date of HCC diagnosis, date of emigration from the study area, date of death, or end of the study period, whichever occurred first. For subjects who withdrew from or were lost to follow-up, the date of withdrawal and the last confirmed date of presence, respectively, were used as the date of censor.

The relative risk of HCC associated with metabolic factors was described using hazard ratios (HRs) and 95% confidence intervals (CIs). Analyses were conducted among total subjects and among those who were hepatitis virus-positive. The Cox proportional hazards model was employed as a control for potential confounding factors, namely, age at baseline (5-year age categories), area (10 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150 to <300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3–4 days/week, and daily (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous), and HCV (anti-HCV-negative, -positive) and HBV infection status (HBsAg-negative, -positive). These variables, obtained from the questionnaire, are either known or suspected from previous studies as risk factors for HCC. Sex, age, and area were treated as strata to allow for a different baseline hazard for each stratum. Testing of the proportional hazards assumption by Schoenfeld and scaled Schoenfeld residuals found no violation of proportionality. In addition, we evaluated whether the effect of overweight and high glucose level influenced each other using a test of interaction by entering into the model multiplicative interaction terms between respective factors. All statistical analyses were performed using Stata 10 (Stata Corporation, College Station, TX) [36].

Results

During 222,800 person-years of follow-up (average follow-up period: 12.7 years) for 17,590 subjects (6,092 men and 11,498 women), a total of 102 cases of newly diagnosed HCC (67 men and 35 women) were identified and included in the analyses.

According to the definition of the respective metabolic factors, 59% of the study subjects had high blood pressure, 21% had high glucose, 23% had low HDL-cholesterol, 24% had high triglycerides, and 31% were overweight. As a consequence, 22% were categorized as having ≥3 metabolic factors, and 16% as having ≥2 factors in addition to being overweight (Table 1).

HRs and CIs of HCC according to the presence of metabolic factors among total subjects are shown in Table 2. The presence of metabolic factors was associated with a significantly increased risk of HCC [HR = 1.68, CI = 1.06–2.66 (≥3 factors); HR = 2.14, CI = 1.27–3.61 (≥2 factors in addition to being overweight)]. HCC was positively associated with components of metabolic factors, namely, high glucose (HR = 1.75, CI = 1.11–2.74) and overweight (HR = 2.22, CI = 1.42–3.48).

When analyzed by sex, a significantly increased risk with the presence of metabolic factors in the aggregate was observed only in men. Increased risk in men was also seen with high glucose and overweight. In women, no clear association with metabolic factors was seen except for a significant increase in risk by overweight (data not shown).

When analyses were limited to subjects with HCV infection (Table 3), results were similar to those among total subjects, although the risk of high glucose was more

Table 1 Baseline characteristics of study subjects ($n = 17,590$)

	Total subjects	HCV-antibody and HBsAg negative subjects	HCV-antibody positive and HBsAg negative subjects	HCV-antibody negative and HBsAg positive subjects	HCV-antibody and HBsAg positive subjects
Number of subjects	17,590	16,213	939	419	19
Total person-years	222,800.6	206,239.1	11,032.9	5,306.3	222.3
Age (mean)	57.0	56.9	59.4	55.6	56.6
Men (%)	34.6	34.0	42.3	42.0	31.6
Smoking status (%)					
Never	71.4	72.2	58.4	69.5	68.4
Past	11.5	11.3	15.1	11.7	5.3
Current	17.1	16.5	26.5	18.9	26.3
Weekly ethanol intake (%)					
Past	2.0	1.8	6.0	1.7	63.2
Never	61.6	62.0	55.4	59.0	5.3
<weekly	6.3	6.3	6.2	6.9	10.5
<150 g per week	15.1	14.9	17.9	14.8	10.5
150 to <300 g per week	8.1	8.1	8.9	7.6	10.5
≥300 g per week	6.9	6.9	5.6	10.0	0.0
Coffee intake (%)					
Almost never	33.2	33.1	35.7	31.0	31.6
1–2 days per week	19.8	19.7	21.1	18.8	10.5
3–4 days per week	10.7	10.6	10.9	14.1	5.3
1–2 cups per day	27.5	27.7	24.6	24.6	42.1
3–4 cups per day	7.1	7.1	6.2	9.1	10.5
≥5 cups per day	1.8	1.8	1.6	2.4	0.0
Serum total cholesterol (mg/dl) (mean)	203.4	204.5	190.0	191.1	193.2
Metabolic factors in the aggregate (%)					
≥3 factors	22.2	22.3	21.5	18.1	15.8
≥2 factors in addition to being overweight	16.1	16.3	13.7	13.1	15.8
Component of metabolic factors (%)					
High blood pressure	59.3	59.0	58.9	61.8	57.9
High glucose	20.7	20.5	23.9	21.0	21.1
Low HDL-cholesterol	23.3	23.2	26.6	19.6	15.8
High triglycerides	23.6	24.1	18.6	15.0	21.1
Overweight	30.8	31.0	25.8	32.9	52.6

attenuated and the risk of overweight was more clearly observed. Likewise, those who were negative for both HCV- and HBV infection revealed a similar tendency to those who were infection-positive, albeit without statistical significance.

Additional analysis was conducted to determine the presence of the effect of BMI and effect modification between overweight and high glucose (Table 4). Increased BMI was associated with HCC in both genders of all subjects and those with HCV infection. The association was more clearly observed in men than in women. The presence of both high glucose and overweight significantly increased the risk of HCC, although no significant effect due to modification between overweight and high glucose level was observed.

Discussion

In this prospective cohort study among a large Japanese population, we found that the presence of metabolic factors in the aggregate predicted the subsequent risk of HCC in men, including those with HCV infection. Our results also confirmed that the main contributors to the effect of

Table 2 Hazard ratios (HRs) and 95% CIs of hepatocellular carcinoma according to the metabolic factors[a]

	Number of subjects	Number of cases	Person-years	HR	(CI)
Components of metabolic factors					
High blood pressure					
Absent	7,156	35	90,694	1.00	
Present	10,434	67	132,107	0.97	(0.62–1.53)
High glucose					
Absent	13,950	65	177,493	1.00	
Present	3,640	37	45,307	1.75	(1.11–2.74)
Low HDL-cholesterol					
Absent	13,487	70	170,673	1.00	
Present	4,103	32	52,128	1.17	(0.72–1.92)
High triglycerides					
Absent	13,442	87	170,277	1.00	
Present	4,148	15	52,523	0.75	(0.40–1.39)
Overweight					
Absent	12,180	64	153,362	1.00	
Present	5,410	38	69,438	2.22	(1.42–3.48)
Metabolic factors in the aggregate					
≥3 factors					
Absent	13,692	73	173,316	1.00	
Present	3,898	29	49,485	1.68	(1.06–2.66)
≥2 factors in addition to being overweight					
Absent	14,756	81	186,608	1.00	
Present	2,834	21	36,192	2.14	(1.27–3.61)

[a] Model includes gender (stratified, men and women combined only), age (stratified, 5-year age categories), area (stratified, 6 PHC areas), smoking status (never, past, current), weekly ethanol intake (past, never, <weekly, <150 g per week, 150 to <300 g per week, ≥300 g per week), coffee intake (never, 1–2 days/week, 3–4 days/week, everyday (1–2 cups/day, ≥3 cups/day), total cholesterol (mg/dl, continuous) and HCV infection status (anti-HCV antibody negative, positive) and HBV infection status (HbsAg negative, positive) and individual components of metabolic syndrome, namely, high blood pressure, high glucose, low HDL-cholesterol, high triglycerides, and overweight (yes, no)

metabolic factors on HCC were overweight and a high glucose state.

Previous epidemiological observations on the effect of metabolic factors in the aggregate on the risk of HCC are scarce [9, 10]. Results have generally shown positive association with metabolic factors in the aggregate, although one [9] did not account for hepatitis virus infection status, and another [10] lacked information on some of the components of metabolic factors and provided results only for subjects without infection. Meanwhile, a number of epidemiological studies have implicated diabetes as a risk factor for HCC [4, 10–20]. Obesity is the most important risk factor for diabetes, and diabetes and obesity are highly related events [37]. A number of epidemiological studies have reported an association between obesity and HCC [10, 21–26], most of which found a significant positive association in men but a weaker positive association in women. The only two studies accounting for hepatitis virus infection status found a significant positive association among those with HCV infection [10, 21], albeit that results for men and women were combined.

The biological mechanism by which metabolic factors leads to HCC has not been fully clarified. One suggested candidate is that obesity leads to insulin resistance and steatosis, which are associated with the release of inflammatory mediators such as tumor necrosis factor (TNF)-α in the liver. This would in turn enhance the production of cytokines, including interleukin (IL)-6 and IL-8, leading to steatohepatitis or NASH [15]. On this basis, obesity and diabetes cause hepatic inflammation, leading to oxidative stress and lipid peroxidation, subsequently resulting in hepatic injury, fibrosis, and eventual cirrhosis and HCC [37]. Several studies have also suggested a synergistic effect of diabetes with viral hepatitis [20] and alcohol intake [15, 16, 20].

It is also known that the liver plays a key role in serum lipoprotein synthesis and metabolism, and impaired lipid metabolism is often found in patients with chronic liver diseases [38]. This finding is supported by several cross-sectional studies among HCV-positive subjects [39, 40]. With metabolic syndrome, free fatty acids (FFAs) are released in abundance from an expanded adipose tissue