Subjects were asked to sit calmly and without talking for at least 2 min before measurement, with their legs uncrossed and their arms crossed at heart level.

Medical history, smoking status and anthropometric data were also collected at the annual health check-up. Classification as hypertensive or normotensive was based on the results of the health check-up. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Outcomes and statistical analysis

The effects of dietary intervention were examined using data from the first half of the study; that is, the group receiving dietary intervention in the first year as the intervention group. Because follow-up study after termination of the intervention suggested that the effects of intervention on diet were maintained well over 4 years, the decision was made to simplify assessment by excluding the data from the second half of the study. Subjects were excluded from the analysis of dietary data if they met either of the following criteria: (1) the DHQ was incomplete for either the pre- (baseline) or post-intervention (year 1); and (2) estimated energy intake was less than 50% of the energy requirement for a sedentary lifestyle or greater than 150% of that for a vigorous lifestyle.

Primary study outcome was the effect of intervention during the first year, namely the difference in changes between the intervention and control groups. Mean daily intakes of energy, targeted nutrients and mean urinary sodium at baseline and year 1 were calculated, with values at each point for fruits and vegetables, as well as alcohol, carotene, and vitamin C, transformed by the natural logarithm before calculation, to account for the skewing of distribution to the right. Mean values of variables for the groups at baseline were compared by the *t*-test. Proportions at baseline were tested by the χ^2 test. Differences from baseline to year 1 within groups are presented with 95% confidence intervals (95% CI). Analyses of covariance (ANCOVA) were conducted to investigate differences in outcome measure at year 1 between the randomized groups. Baseline values of each variable were included as covariates. For BP analysis, baseline BP and change in alcohol intake and body weight were included as covariates. All analyses were done with SAS statistical software (SAS Institute Inc., Cary, North Carolina, USA, version 8.0).

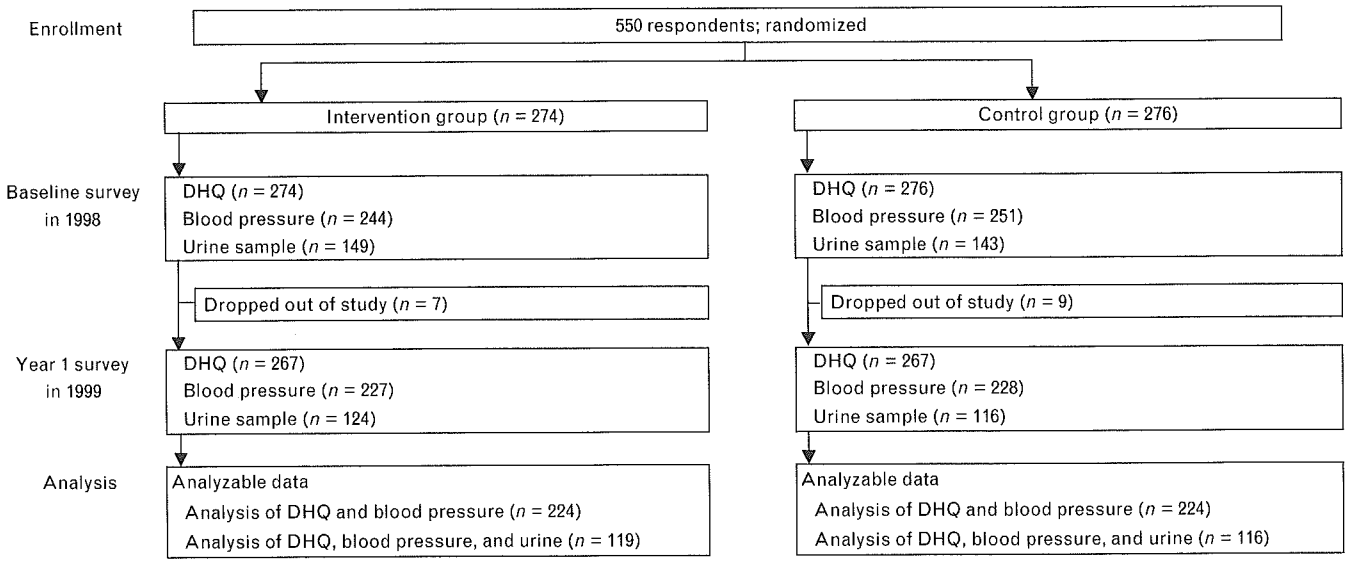
Results

Baseline characteristics

A total of 292 urine samples were obtained from 550 respondents who completed the DHQ at baseline (Fig. 1), and 240 samples from 534 subjects who completed the DHQ at year 1. Analysis included 235 and 448 subjects with and without urinary data, respectively.

Table 1 shows baseline variables for the intervention and control groups. Mean age of participants was 56.4 years. Mean systolic BP (SBP) and diastolic BP (DBP) did not statistically differ between the groups. Among participants, 11% (26 and 23 subjects in the intervention and control group, respectively) were receiving antihypertensive drug treatment at the beginning of the trial. Antihypertensive medication status of these subjects

Fig. 1



Number of study subjects. DHQ, diet history questionnaire.

Table 1 Subject characteristics at baseline

	Intervention group ($n = 224$)	Control group ($n = 224$)	P^a
Age (years)[b]	56.3 (41.2, 71.4)	56.4 (40.5, 72.4)	0.863
Sex (% female)	68.3	67.0	0.762
Body height (cm)[b]	154.9 (140.6, 169.2)	155.2 (139.1, 171.4)	0.978
Body weight (kg)[b]	56.7 (39.5, 73.8)	56.0 (39.1, 72.9)	0.996
Body mass index (kg/m^2)[b]	23.6 (17.9, 29.3)	23.2 (17.6, 28.8)	0.949
Blood pressure (mmHg)[b]			
Systolic blood pressure	127.9 (93.2, 162.5)	128.0 (97.4, 158.5)	0.955
Diastolic blood pressure	75.9 (53.9, 97.8)	76.3 (55.9, 96.6)	0.720
Alcohol drinker (%)	38.8	40.2	0.772
Hypertension (%)	23.7	24.1	0.912
On antihypertensives (%)	11.6	10.3	0.650
Diabetes (%)	3.6	3.1	0.793
Hyperlipidemia (%)	5.8	10.3	0.082

[a]P value for comparison between groups. [b]Values are mean and 95% confidence intervals.

did not change throughout the trial (data not shown). There were no statistically significant differences between the groups in age and sex distribution or other baseline variables.

Effect of intervention on lifestyle factors and dietary variables

Mean body weight and lifestyle factors and their changes from baseline to year 1 are presented in Table 2. No statistically significant change was observed between the groups. Daily intake of energy and nutrients and their changes are also presented in Table 2. At year 1, intake of fruit and vegetables and of dietary carotene and vitamin C increased significantly more in the intervention group ($P < 0.05$). Sodium intake in the intervention group decreased by 15 mmol/day (95% CI: −26, −4), but increased by 11 mmol/day (−0, +22) in the control group. This difference in change between the two groups was statistically significant ($P = 0.002$). Mean urinary excretion of sodium and potassium and the corresponding daily intake are shown in Table 3. Excretion and intake of sodium in the intervention group decreased by 49 (95% CI: −62, −36) and 11 mmol/day (−25, +4), respectively. This difference in change between the two groups was statistically significant ($P < 0.001$).

Effects of intervention on BP

Table 4 shows that SBP in the intervention group decreased from 127.9 to 125.2 mmHg (−2.7 mmHg change; 95% CI: −4.6, −0.8), but in the control group increased from 128.0 to 128.5 mmHg (+0.5 mmHg change; −1.3, +2.3), with this difference in change between the groups being statistically significant ($P < 0.01$). DBP changed from 75.9 to 74.8 mmHg (−1.0 mmHg change; 95% CI: −2.4, +0.3) in the intervention and from 76.3 to 75.9 mmHg (−0.3 mmHg change; −1.7, +1.1) in the control group. This difference in change between the groups was not statistically significant.

Data for the subgroup of subjects from whom urine was collected were analyzed separately. Results showed no difference in baseline SBP and DBP between those with and without urine collection (data not shown). SBP changed for urine collectors by −3.0 mmHg (95% CI: −5.7, −0.2) in the intervention group, whereas it changed by +0.3 mmHg (−2.5, +3.1) in the control group. This difference in change between the groups being statistically significant ($P < 0.05$).

BP data were also analyzed by hypertensive status. In the hypertensive subjects, SBP changed by −5.6 mmHg (95% CI: −9.3, −2.0) in the intervention group, whereas it changed by +1.4 mmHg (95% CI: −3.6, 6.3) in the control group. This difference in change between the groups was statistically significant ($P < 0.05$). In normotensive subjects, the decrease in SBP was also greater in the intervention group compared to the control group, but this difference in change did not reach the level of statistical significance ($P = 0.075$). Further, no statistically significant changes in DBP were observed between the two groups in either subgroup analysis.

Discussion

This 1-year dietary, moderate-intensity, community-based intervention trial demonstrated a significant decrease in SBP level. A greater decrease in average dietary intake and urinary excretion of sodium was seen in the intervention group than in the control group. An increase in fruit and vegetable intake was accompanied by an increase in carotene and vitamin C intake.

Several community-based, large-scale, randomized trials on the effects of dietary intervention on BP have been reported to date. However, the variability of lifestyle intervention topics and their intensity makes it difficult to compare the BP changes achieved. Further, most of these previous studies targeted only hypertensive subjects.

Changes in BP and urinary sodium

Brunner *et al.* [14] performed a meta-analysis of randomized controlled trials designed to investigate the primary prevention of chronic diseases, and evaluated the effects

Table 2 Body weight and nutrient and food intakes at each point

	Intervention group (n = 224)			Control group (n = 224)				
	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[c] (95% CI)	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[c] (95% CI)	Adjusted between-group difference in change[d] (95% CI)	Adjusted P value[e]
Body weight (kg)	56.7 (39.5, 73.8)	56.5 (39.4, 73.7)	−0.1 (−0.3, 0.1)	56.0 (39.1, 72.9)	55.9 (39.2, 72.7)	−0.1 (−0.4, 0.1)	0.0 (−0.3, 0.3)	0.907
Moderate physical activity[a] no. (%)	223 (99.6%)	223 (99.6%)	0 (0%)	224 (100%)	224 (100%)	0 (0%)	0 (0%)	–
Current smoker[a] no. (%)	22 (9.8%)	22 (9.8%)	0 (0%)	26 (11.6%)	26 (11.6%)	0 (0%)	0 (0%)	–
Energy intake (MJ/day)	8.56 (3.43, 13.68)	8.44 (3.46, 13.41)	−0.12 (−0.38, 0.15)	8.15 (3.36, 12.96)	8.30 (3.40, 13.20)	0.16 (−0.13, 0.44)	−0.13 (−0.49, 0.22)	0.454
Alcohol (g/day)	3.5[b] (−1.6, 76.4)	3.0[b] (−1.6, 57.7)	−2.9 (−4.7, −1.2)	3.6[b] (−1.6, 76.2)	3.2[b] (−1.6, 65.7)	−1.6 (−3.7, 0.5)	−1.3 (−3.6, 1.0)	0.270
Nutrient intake								
Carotene (μg/day)	2159[b] (507, 9196)	2622[b] (677, 10156)	468 (166, 771)	1789[b] (331, 9676)	1944[b] (377, 10036)	170 (−77, 418)	521 (184, 858)	0.003
Vitamin C (mg/day)	107[b] (32, 358)	123[b] (42, 362)	15 (3, 26)	95[b] (24, 376)	100[b] (27, 364)	1 (−9, 12)	19 (6, 31)	0.003
Sodium (mmol/day)	237 (76, 397)	222 (54, 390)	−15 (−26, −4)	229 (64, 395)	240 (61, 420)	11 (−0, 22)	−23 (−37, −8)	0.002
Potassium (mmol/day)	71 (18, 123)	73 (18, 128)	2 (−1, 6)	65 (17, 113)	66 (20, 113)	1 (−2, 4)	4 (−1, 8)	0.081
Dietary fiber (g/day)	15.6 (3.1, 28.0)	16.2 (4.1, 28.3)	0.6 (−0.2, 1.5)	14.3 (3.2, 25.4)	14.6 (4.2, 25.1)	0.3 (−0.4, 1.0)	1.0 (0.0, 1.9)	0.040
Calcium (mg/day)	691 (59, 1323)	690 (106, 1274)	−1 (−45, 43)	621 (129, 1113)	663 (83, 1244)	42 (6, 78)	−7 (−56, 43)	0.792
Food intake								
Vegetables (g/day)	252.8[b] (72.2, 879.3)	269.3[b] (85.0, 848.1)	15.1 (−12.8, 42.9)	226.4[b] (62.4, 815.2)	227.3[b] (65.7, 781.0)	−2.1 (−19.7, 15.5)	34.2 (5.3, 63.0)	0.020
Fruits (g/day)	63.3[b] (7.5, 486.9)	84.5[b] (12.4, 543.0)	24.3 (11.5, 37.1)	59.3[b] (6.2, 503.5)	63.1[b] (6.8, 523.8)	2.0 (−10.0, 13.9)	23.1 (7.9, 38.4)	0.003

[a]Number and percentage of subjects. [b]Mean values at each point were transformed by the natural logarithm before computation because of the skewed distributions. They were back-transformed to show means and 95% confidence intervals (CIs). [c]Difference between baseline and year 1. [d]Difference between intervention group and control group in change after adjustment for baseline intake. [e]P values for comparison of mean at year 1 between the intervention group and control group by ANCOVA after adjustment for baseline intake.

Table 3 Dietary intake and 48-h urinary excretion of sodium and potassium [means and 95% confidence intervals (CIs)] among subjects who completed urine collection at two points

	Intervention group (n = 119)			Control group (n = 116)				
	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[b] (95% CI)	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[b] (95% CI)	Adjusted between-group difference in change[c] (95% CI)	Adjusted P value[d]
Sodium (mmol/day)								
Dietary intake	242 (85, 398)	229 (65, 393)	−13 (−29, 3)	235 (78, 392)	247 (65, 428)	12 (−5, 28)	−21 (−41, −1)	0.040
Urinary excretion[a]	248 (103, 393)	199 (62, 335)	−49 (−62, −36)	248 (94, 402)	237 (50, 424)	−11 (−25, 4)	−39 (−56, −21)	<0.001
Potassium (mmol/day)								
Dietary intake	73 (22, 123)	75 (25, 125)	2 (−3, 7)	69 (20, 117)	69 (22, 117)	1 (−4, 5)	4 (−2, 9)	0.204
Urinary excretion[a]	66 (26, 107)	59 (18, 100)	−7 (−11, −3)	66 (27, 105)	61 (17, 105)	−4 (−8, −1)	−2 (−7, 3)	0.408

[a]Expected intake was considered to be observed urinary excretion divided by 0.86 for sodium and 0.77 for potassium. See text for details. [b]Difference between baseline and year 1. [c]Difference between intervention group and control group in change after adjustment for baseline value. [d]P values for comparison of mean at year1 between the intervention group and control group by ANCOVA after adjustment for baseline value.

Table 4 Blood pressure [mean and 95% confidence interval (CI)] at two points

	Intervention group			Control group				
	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[a] (95% CI)	Baseline Mean (95% CI)	Year 1 Mean (95% CI)	Change[a] (95% CI)	Adjusted between-group difference in change[b] (95% CI)	Adjusted *P* value[c]
All subjects		($n = 224$)			($n = 224$)			
SBP (mmHg)	127.9 (93.2, 162.5)	125.2 (93.7, 156.7)	−2.7 (−4.6, −0.8)	128.0 (97.4, 158.5)	128.5 (99.0, 158.0)	0.5 (−1.3, 2.3)	−3.1 (−5.4, −0.9)	0.007
DBP (mmHg)	75.9 (53.9, 97.8)	74.8 (53.3, 96.4)	−1.0 (−2.4, 0.3)	76.3 (55.9, 96.6)	75.9 (55.9, 95.9)	−0.3 (−1.7, 1.1)	−0.9 (−2.6, 0.8)	0.307
Urine collection		($n = 119$)			($n = 116$)			
SBP (mmHg)	128.0 (91.6, 164.3)	125.0 (92.9, 157.2)	−3.0 (−5.7, −0.2)	128.4 (98.6, 158.2)	128.7 (98.1, 159.3)	0.3 (−2.5, 3.1)	−3.4 (−6.8, −0.0)	0.048
DBP (mmHg)	75.8 (53.5, 98.2)	74.5 (53.8, 95.2)	−1.3 (−3.1, 0.4)	76.8 (57.6, 96.1)	75.8 (56.5, 95.0)	−1.1 (−3.0, 0.9)	−0.8 (−3.0, 1.5)	0.502
Normotensive		($n = 171$)			($n = 170$)			
SBP (mmHg)	123.3 (91.2, 155.4)	121.6 (91.8, 151.3)	−1.8 (−4.0, 0.4)	124.1 (98.2, 150.0)	124.3 (98.3, 150.3)	0.2 (−1.6, 2.1)	−2.3 (−4.7, 0.2)	0.075
DBP (mmHg)	73.6 (52.6, 94.5)	72.5 (52.6, 92.5)	−1.1 (−2.7, 0.5)	74.7 (55.6, 93.8)	74.2 (54.8, 93.6)	−0.5 (−2.1, 1.1)	−1.2 (−3.1, 0.7)	0.233
Hypertensive		($n = 53$)			($n = 54$)			
SBP (mmHg)	142.5 (116.2, 168.8)	136.9 (111.4, 162.3)	−5.6 (−9.3, −2.0)	140.2 (108.4, 172.0)	141.6 (116.6, 166.5)	1.4 (−3.6, 6.3)	−5.2 (−9.9, −0.4)	0.032
DBP (mmHg)	83.3 (64.5, 102.0)	82.4 (62.5, 102.3)	−0.9 (−3.3, 1.5)	81.1 (59.9, 102.3)	81.3 (63.0, 99.6)	0.2 (−2.9, 3.3)	0.1 (−3.3, 3.4)	0.971

[a]Difference between baseline and year 1. [b]Difference between intervention group and control group in change after adjustment for baseline values and change in alcohol intake and body weight. [c]*P* values for comparison of mean at year 1 between the intervention group and control group by ANCOVA after adjustment for baseline values and changes in alcohol intake and body weight. SBP, systolic blood pressure; DBP, diastolic blood pressure.

of dietary change on BP in free-living subjects. This meta-analysis included relatively intensive dietary interventions such as monthly group sessions and several individual counseling sessions. Among the four studies which aimed to reduce sodium intake, overall mean net urinary sodium reduction was 32 mmol/24 h. Further, the mean net BP changes over 9–18 months were −1.9 mmHg (95% CI: −3.0, −0.8) for SBP and −1.2 mmHg (−2.6, 0.2) for DBP. The net changes in BP and urinary sodium excretion seen in the present study were slightly greater than the results of this meta-analysis.

Change in BP among hypertensive subjects

Analysis of subjects by hypertensive status showed that the effect of dietary modification on BP was greater in subjects of the hypertensive subgroup. The most recent meta-analysis of clinical trials of salt reduction [15] showed a 4.96/2.73 mmHg decrease in hypertensives ($P < 0.001$ for both SBP and DBP). The effect on SBP in the present hypertensive subjects was comparable with these previous results. Dietary modification might prevent or delay the initiation of medication in hypertensive subjects with BP levels that straddle the threshold for antihypertensive medication.

Changes in BP and intake of other nutrients and lifestyle factors

The present study focused on the increase in the intake of vitamin C and carotene by recommendation of more fruits and vegetables. Results showed a moderate increase in carotene, vitamin C and dietary fiber intake, but not in potassium or calcium. Previous observational studies have reported significant inverse associations between BP and the intake of vitamin C, dietary fiber, potassium, magnesium and calcium [16–19]. The effectiveness of these nutrients has also been confirmed in clinical trials of dietary fiber, potassium, magnesium and calcium [20–23]. Furthermore, lifestyle factors such as physical activity, weight loss, alcohol consumption and smoking also influence BP level [24–26]. We did not observe changes in these variables. The decrease in BP seen in the present study might be attributable at least to some extent to increases in the intake of vitamin C and dietary fiber.

Changes in BP and fruit and vegetable intake

The present study focused on the use of fruits and vegetables to increase carotene and vitamin C intake.

Several previous clinical studies have examined the effect of dietary intervention on BP. The DASH trial, a well-controlled, randomized, clinical trial [7] to assess the effects of dietary patterns on BP, showed a decrease in SBP of 2.8 mmHg and in DBP by 1.1 mmHg by an increase in dietary fruit and vegetable intake for 8 weeks. In a subsequent study [27], this hypotensive effect of the

DASH diet was enhanced by its combination with a reduced sodium diet (100 and 50 mmol/day). The results of the present study support those of the DASH trials by showing similar, albeit somewhat weaker, results in a free-living, general population.

Further, Nowson *et al.* [28] conducted a cross-over dietary intervention study using a community-living subject. They reported a significant decrease in BP by a low-sodium, high-potassium diet and a DASH-type diet (DASH diet with moderate sodium reduction). The tendency of the results was similar to those of the present study, but the size of the effect was greater. However, the study population in their study was smaller ($n = 94$), the study period shorter (4 weeks), and the intervention more intensive (bi-weekly contact) than in the present study. Salt-free bread, salt-free margarine or both were provided to the intervention subjects. In contrast, no food was provided in the present study. The method used in the present study appears to be more practicable for use in community settings than that in the study of Nowson *et al.* [28].

Study limitations

Because this study was an open trial, the possibility of interaction between the intervention and control groups, such as information exchange, cannot be ruled out. In the control group, however, no statistically significant change in targeted nutrients and foods between the baseline and year 1 points was observed, suggesting that any interaction between the groups may have been negligible. Nevertheless, the possibility of some general information exchange remains, and the results should therefore be interpreted with caution.

To examine a practical model for population-based lifestyle improvement intervention, our present intervention study was performed in a primary health care setting rather than an academic center setting. Measurement of BP was conducted at the annual health check-up as a routine component of that check-up, and thus only a single measurement was done instead of multiple measurement. Nevertheless, conditions between the two groups were the same.

Because they had been previously exposed to various public health campaigns in the study area on the importance of decreasing salt intake, the present study subjects were relatively well-motivated to reduce their salt intake [29]. Moreover, they were provided further information about the unfavorable effect of dietary sodium on health prior to the start of the study. We therefore presume that they were more receptive to the message to decrease sodium given in this study. The decrease in sodium and consequent decrease in BP observed in this trial indicates the effectiveness of this intervention method for motivated persons. Further studies are necessary to determine whether this intervention method is equally effective on dietary and BP modification in other populations.

In conclusion, these findings indicate that the effects of dietary interventions undertaken to reduce the intake of sodium and increase that of fruit and vegetables may be expected to decrease BP level in free-living populations. The present randomized, controlled trial involved a relatively large number of free-living subjects and examined the change in dietary habits and BP over 1 year. The intervention method used here may represent an efficient and practicable model for population-based BP improvement in common primary care settings.

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Active and passive smoking and breast cancer risk in middle-aged Japanese women

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To examine the hypothesis that tobacco smoke is associated with the risk of female breast cancer, we estimated the relative risks of active and passive smoke in middle-aged Japanese women in a population-based prospective study. The cohort consisted of residents in 4 public health center areas, aged 40 to 59 years. A self-administered questionnaire survey was conducted in 1990. This analysis included 21,805 subjects, 180 of whom had developed breast cancer by December 31, 1999. When the reference was defined as never-active smokers without passive smoking, adjusted relative risks (RRs) were 1.9 (95% confidence interval [CI] = 1.0–3.6) in current active smokers, 1.2 (95% CI = 0.4–4.0) in ex-active smokers and 1.2 (95% CI = 0.8–1.6) in never-active smokers with passive smoking. The elevated risk for ever-smokers was clearly observed in premenopausal women at baseline (RR = 3.9, 95% CI = 1.5–9.9) but not in postmenopausal women (RR = 1.1, 95% CI = 0.5–2.5). In never-active smokers, the adjusted RR for passive smoking, residential or occupational/public tobacco smoke exposure was 1.1 (95% CI = 0.8–1.6). In premenopausal women, passive smoking increased the risk (RR = 2.6; 95% CI = 1.3–5.2) but not in postmenopausal women (RR = 0.7; 95% CI = 0.4–1.0). We conclude that tobacco smoking increases the risk of female breast cancer in premenopausal women.

Key words: breast neoplasms; smoking; passive smoking; cohort study

Because most established risk factors for female breast cancer cannot be modified, the etiological role of tobacco smoking has been of interest in the public health field. As shown in a recent general comment by WHO's Executive Director, the link between smoking and breast cancer has been elusive; some studies have suggested a positive link, others found no relationship and a few have suggested that smoking has protective effects.[1] A positive association has been observed in some previous case-control studies.[2–7] In contrast, little relationship has been reported by cohort studies.[8–11] Theoretically, a cohort study provides better evidence compared to a case-control study, but the limitations, *e.g.*, reference category and misclassification of smoking habits, in recent cohort studies are still under dispute.[12–15]

Tobacco smoke is well known to contain numerous possible carcinogens.[16] Although they do not directly contact mammary cells, many studies utilizing biomarkers have demonstrated that tobacco-related carcinogens reach human breast tissue.[17–19] On the other hand, antiestrogenic effects of tobacco smoke have been suggested by many published observations.[20–23] Thus, the exposure may decrease the breast cancer risk, especially in postmenopausal women.[24,25]

The objective of our study was to examine the hypothesis that tobacco smoking is associated with the risk of female breast cancer. We estimated the risks of active and passive smoking among middle-aged Japanese women in a population-based cohort study. The influence of tobacco smoke as a breast cancer risk was elucidated by menopausal status at the baseline survey of the study.

Material and methods

Study cohort

The study cohort is part of the Japan Public Health Center (JPHC)-based prospective study on cancer and cardiovascular diseases (JPHC Study, cohort I) established on January 1, 1990. The study population was defined as Japanese residents aged 40–59 years, 27,063 men and 27,435 women, in 14 administrative districts in 4 PHC areas across Japan.[26] After the initiation of the study, 37 women were found to be ineligible and were excluded, leaving 27,398 women eligible for the study. Study procedures were approved by the ethics committee of the National Cancer Center, Tokyo, Japan.

Baseline survey

A self-administered questionnaire was distributed mostly by hand and partly by mail to the subjects in 1990. They were asked about their personal and familial medical histories, smoking habit, alcohol consumption, dietary habits and other lifestyle factors. A total of 22,482 women responded to the survey (82.1% response rate). Although the date of questionnaire completion ranged from January 1990 to May 1992, 54% responded between February 1990 and March 1990. Only 4% of questionnaires were completed after October 1990. The questions on active smoking consisted of current and former smoking status, age at initiation of smoking, average number of cigarettes smoked per day and age at cessation of smoking for former smokers. Questions on passive smoking were in 2 parts: a) "Have you lived with any regular smokers?" and age at exposure (≤ 20 years old, > 20 years old, both) and b) " In places outside the home, *e.g.*, at work, how often are you exposed to environmental tobacco smoke ≥ 1 hr/day?" (almost never, 1 to 3 days/month, 1 to 4 days/week, almost everyday).

Follow-up and identification of breast cancer

We followed the subjects from recruitment until December 31, 1999. In Japan, all death certificates are submitted to a local government office and forwarded to the PHC in the area of residence. Mortality data are then sent to the Ministry of Health, Labour and Welfare and coded for inclusion in the National Vital Statistics. The registration of deaths in Japan is required by the Family Registration Law and is theoretically complete. Therefore, all deaths of the subjects were based upon death certificates from each PHC, when they remained in the original area. Changes in residence status were identified annually through the residential registry in each area. Collection of cancer incidence data and migration data was described in a previous report.[27] Briefly, on January 1, 1990, a specific cancer registry for the JPHC Study was

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established to collect cancer incidence data on the study subjects living within the study area *via* voluntary reports from local major hospitals, on-site visits to the hospitals and records from the prefecture-wide population-based cancer registry, if available (Akita and Nagano Prefectures do not have a prefecture-wide cancer registry). Cancer incidence data were collected only for subjects who were living within the study area. Site of origin and histologic type were coded using the International Classification of Disease for Oncology, second edition (ICD-O-2). By December 31, 1999, 226 new breast cancer cases had been identified. Twelve carcinoma *in situ* were not included among these breast cancer cases. A diagnosis of breast cancer was histologically confirmed in 97% of the cases. The incidence/mortality ratio in the cancer registration was 5.4, and no cases were ascertained by death certificate alone [Death Certificate Only (DCO)]. In 1.1% of cases the subjects' death certificates were used as a supplementary information source for the registry [Death Certificate Notification (DCN)]. The estimated completeness of the registration was 91.8%, which suggested that the completeness for this cohort was reasonably high.[28,29]

Migration data were obtained from residential registries. Among non-case study subjects, 1,837 (6.7%) moved out of the study area and 34 (0.1%) were lost to follow-up within the study period.

Data analysis

From the 22,482 subjects, we excluded 612 more (including 12 breast cancer cases) with a past history of cancer in any site. Consequently, after excluding still another 53 subjects who submitted incomplete information on active or passive smoking status, a total of 21,805 subjects, 180 of whom developed breast cancer, were included in this analysis. Person-years of follow-up were counted from the date of questionnaire completion until the dates of a diagnosis of breast cancer, migration out of the study areas, death or the end of the study (December 31, 1999), whichever came first.

The relative risk (RR) and 95% confidence interval (CI) were estimated by the Cox proportional hazards model, adjusting for age and area according to the SAS PHREG procedure (SAS Institute, Inc., Cary, NC). For further adjustment, we incorporated additional possible confounders into the model; education level (≥ high school and < high school), employment status (employed and unemployed), body mass index (< 22, < 25, and ≥ 25), family history of breast cancer in mother or sisters, history of past benign breast disease, age at menarche, number of births (0, ≥ 1), menopausal status (pre and post), hormone use and alcohol consumption per week (< once/week, < 250 g/week, ≥ 250 g/week). Concerning body mass index and the number of births, influence on the estimates was similar between the categorical and continuous variables. Height, weight, fruit and vegetable intake and physical activity had little influence on the estimates and thus were omitted from the adjustment in the final analysis. Breast-feeding was not incorporated in the adjustment factors because it was not included in the questionnaire. We coded current occupations recorded in an open-end column in the questionnaire according to a major occupational category (Standard Occupational Classification for Japan, the third revision of 1997, Statistic Bureau, The Ministry of Public Management). The occupational categories consisted of professionals and technicians; managers; clerks; shop and market sales workers; service workers; security workers; agricultural, forestry and fishery workers; transport and communication workers; assemblers and manual laborers; workers unclassified and unemployed. Most agricultural, forestry and fishery workers were farmers. In the analysis concerning active smoking, passive smoking was defined as a history of exposure to residential sidestream smoke in any period or exposure to sidestream smoke (almost everyday) in any occupational and/or public setting.

After excluding from the analyses 6 cases whose pathological information was uncertain, we obtained results similar to those presented.

Results

Among the 21,805 women, the prevalence of current, ex- and never-active smokers was 5.7%, 1.7% and 92.6%, respectively. Among never-active smokers, 69% reported that they had been exposed to sidestream smoke (Table I). Table II compares known risk factors and possible confounders for breast cancer among 4 categories of smoking status. These factors included characteristics reported in the literature to be risk factors, and most of them served as adjustment factors in further statistical analyses. Table III shows RRs of incidence according to active smoking. Without taking account of passive smoking in the reference category, the adjusted RR for current active smokers was 1.7 (95% CI = 1.0–3.1). When the reference condition was defined as never-active smokers without passive smoking, a 2-fold risk was observed among current active smokers (adjusted RR = 1.9; 95% CI = 1.0–3.6). Stratified analyses by employment status showed the following adjusted RRs; 1.0 (95% CI = 0.5–2.0) for unemployed women with passive smoking, 0.8 (95% CI = 0.2–3.9) for unemployed women with active smoking, 1.2 (95% CI = 0.8–1.9) for employed women with passive smoking and 2.3 (95% CI = 1.1–4.8) for employed women with active smoking. After omitting the first 3 years after the study baseline to exclude possibly ill subjects, we observed similar results (data not shown).

In premenopausal women at baseline, ever-active smokers showed a 4-fold increased risk (adjusted RR = 3.9; 95% CI = 1.5–9.9); never-active smokers with passive smoking also exhibited a significantly increased risk (adjusted RR = 2.6; 95% CI = 1.3–5.2)compared to never-active smokers without passive smoking. Stratified analyses by employment status showed increased risk for active and passive smoking in both unemployed and employed women; adjusted RR = 4.4 (95% CI = 0.6–34.6) for unemployed women with passive smoking; 7.9 (95% CI = 0.7–90.8) for unemployed women with ever-active smoking, 2.3 (95% CI = 1.1–4.9) for employed women with passive smoking and 3.3 (95% CI = 1.2–9.4) for employed women with ever-active smoking.

In postmenopausal women at baseline, no significant increased risk was observed for ever-active smokers (adjusted RR = 1.1; 95% CI = 0.5–2.5). Stratified analyses by employment status showed the following adjusted RRs; 0.6 (95% CI = 0.3–1.3) for unemployed women with passive smoking, 0.3 (95% CI = 0.04–2.6) unemployed women with ever-active smoking, 0.7 (95% CI = 0.4–1.2) for employed women with passive smoking and 1.5 (95% CI = 0.6–3.9) for employed women with ever-active smoking. When ex-smokers were eliminated from the statistical model because of the small number of cases and person-years, the risk of smoking remained essentially unchanged (data not shown).

TABLE I – SMOKING STATUS IN FEMALE STUDY SUBJECTS; JPHC STUDY COHORT I

Passive smoking	Active smoking		
	Never-smokers (n = 20169)	Ex-smokers (n = 374)	Current smokers (n = 1238)
Residential passive smoking (%)[1]			
Never	6175 (31.0)	79 (21.4)	234 (19.1)
Ever			
Before age 20	2231 (11.2)	54 (14.6)	225 (18.4)
After age 20	6957 (35.0)	136 (36.8)	444 (36.3)
Both	4536 (22.8)	101 (27.3)	320 (26.2)
Passive smoking in occupational and/or public settings (%)[2]			
Almost never	13626 (68.0)	199 (53.6)	553 (44.8)
1–3 days/month	1534 (7.7)	29 (7.8)	76 (6.2)
1–4 days/week	1057 (5.3)	25 (6.7)	76 (6.2)
Almost everyday	3811 (19.0)	118 (31.8)	529 (42.9)

[1]Missing and unavailable answers were omitted from the calculation; 270 in never-smokers, 4 in ex-smokers, 15 in current smokers.– [2]Missing were omitted from the calculation; 141 in never-smokers, 3 in ex-smokers, 4 in current smokers.

TABLE II – DISTRIBUTION OF KNOWN RISK FACTORS AND POSSIBLE CONFOUNDERS FOR BREAST CANCER BY SMOKING STATUS: JPHC STUDY COHORT 1

	Never-smokers		Ex-smokers (n = 374)	Current smokers (n = 1238)	p for trend[1]
	Without passive smoking (n = 5660)	With passive smoking (n = 14533)			
Age (mean)	49.9	49.6	49.1	48.6	<0.0001
Occupation, farmer (%)[2]	1281 (23.4)	3,014 (21.2)	46 (12.5)	131 (10.9)	<0.0001
Occupation, unemployed (%)[2]	2850 (52.1)	6,423 (45.2)	164 (44.6)	494 (41.2)	<0.0001
Education (> high school, %)[2]	597 (10.9)	1,746 (12.4)	68 (18.7)	140 (11.8)	0.02
Height (mean)	151.1	151.8	152.3	152.2	<0.0001
Weight (mean)	54.3	54.2	55.8	54.2	0.58
Body mass index (mean)	23.7	23.5	24.1	23.3	<0.0001
Family history of breast cancer in mother or sisters (%)[2]	18 (0.3)	90 (0.6)	3 (0.8)	5 (0.4)	0.18
History of past benign breast disease (%)[2]	455 (8.0)	1,525 (10.5)	40 (10.7)	98 (7.9)	0.08
Age at menarche (mean)	14.7	14.6	14.4	14.8	0.30
Parous women (%)[2]	4,922 (93.3)	13,063 (95.2)	307 (89.5)	1,043 (90.7)	0.04
Age at first delivery among parous women (mean)	25.0	24.9	25.5	24.5	<0.0001
Number of deliveries among parous women (mean)	2.9	2.9	2.8	2.9	0.29
Menopausal status (postmenopausal, %)[2]	3,045 (55.2)	7,734 (54.2)	189 (51.9)	602 (49.4)	<0.001
Previous and/or current hormone use (%)[2]	1,114 (21.0)	2,786 (20.4)	82 (23.0)	258 (22.1)	0.58
Alcohol consumption per week (mean grams)	79.2	115.7	164.0	239.3	<0.0001

[1]p for trend was calculated by Cochran-Mantel-Haenszel test.– [2]Missing were omitted from the calculation; 619 in occupation, 743 in education, 53 in family history of breast cancer, 53 in history of past benign breast disease, 1,369 in child birth, 473 in menopausal status and 1,369 in hormone use.

TABLE III – RELATIVE RISK OF FEMALE BREAST CANCER ACCORDING TO ACTIVE SMOKING: 10-YEAR FOLLOW-UP IN JPHC STUDY COHORT 1

Exposure	Number of case	Person-years	RR[1] (95% CI)	RR[2] (95% CI)
Pre-and post-menopausal women at baseline:				
Never-smoker	162	187,063	1.0	1.0
Ex-smoker	4	3,344	1.4 (0.5 to 3.8)	1.1 (0.4 to 3.5)
Current smoker	14	10,901	1.5 (0.9 to 2.6)	1.7 (1.0 to 3.1)
Pre-and post-menopausal women at baseline:				
Never-smoker without passive smoking	40	52,884	1.0	1.0
Never-smoker with passive smoking	122	134,178	1.2 (0.8 to 1.7)	1.1 (0.8 to 1.6)
Ex-smoker	4	3,344	1.6 (0.6 to 4.5)	1.2 (0.4 to 4.0)
Current smoker	14	10,901	1.7 (0.9 to 3.1)	1.9 (1.0 to 3.6)
Premenopausal women at baseline:				
Never-smoker without passive smoking	9	22,982	1.0	1.0
Never-smoker with passive smoking	68	60,272	2.9 (1.4 to 5.8)	2.6 (1.3 to 5.2)
Current- + ex-smoker	11	6,907	4.1 (1.7 to 9.9)	3.9 (1.5 to 9.9)
Postmenopausal women at baseline:				
Never-smoker without passive smoking	31	28,583	1.0	1.0
Never-smoker with passive smoking	52	71,602	0.7 (0.4 to 1.0)	0.6 (0.4 to 1.0)
Current- + ex-smoker	7	7,056	0.9 (0.4 to 2.1)	1.1 (0.5 to 2.5)

[1]Relative risks adjusted for public health center (4 areas) and age (4 5-year age groups).– [2]Relative risks adjusted for public health center, age, employment status (employed and unemployed), education level (≥high school and <high school), body mass index (<22, 22 ≤<25 and ≥25), family history of breast cancer in mother or sisters, history of past benign breast disease, age at menarche, number of births (0 and ≥1), menopausal status (pre and post), hormone use and alcohol consumption per week (<once/week, <250 g/week and ≥250 g/week).

Table IV shows RRs of incidence according to passive smoking status. Adjusted RR for any passive smoking was 1.1 (95% CI = 0.8–1.6). In premenopausal women at baseline, those with any passive smoking revealed a significantly increased risk (adjusted RR = 2.6; 95% CI = 1.3–5.2), and exposure to sidestream smoke in occupational and/or public settings itself showed increased risk (adjusted RR = 2.3; 95% CI = 1.4–3.8). Concerning passive smoking in occupational and/or public settings in premenopausal women, a dose-dependent increase was found (adjusted RR = 1.0 for "almost none"; 0.6 [95% CI = 0.4–2.4] for "1 to 3 days/month", 2.2 [95% CI = 1.4–3.7] for "≥ 1 days/week", p for trend 0.002). Past exposure to sidestream smoke at home did not show an increased risk. Among postmenopausal women at baseline, RRs for passive smoking were 0.7 (95% CI = 0.4–1.0), and those exposed to sidestream smoke in an occupational and/or public setting showed a marginal decreased risk (adjusted RR = 0.5; 95% CI = 0.2–1.0).

Discussion

In the present population-based prospective study of middle-aged Japanese women, an increased risk for active premenopausal smoking women was observed, especially when the reference was defined as never-active smokers without exposure to sidestream smoke. A subgroup analysis revealed that only premenopausal women at the study baseline showed increased risks from passive smoking. These findings were independent of reproductive risk factors and other potential confounders. In previous case-control studies, the risk for active and passive smoking was equivalent,[3,4,6,7] which seems to be implausible. However, the estimated risk for active smoking was larger than that for passive smoking in our study.

Breast cancer risks differ based on menopausal status.[30] Thus, the risk factors and the magnitude of their risk may be different before and after menopause. The etiological roles of endogenous

TABLE IV – RELATIVE RISK OF FEMALE BREAST CANCER ACCORDING TO PASSIVE SMOKING IN FEMALE NEVER-SMOKERS: 10-YEAR FOLLOW-UP IN JPHC STUDY COHORT I

		Passive smoking		
	Never	(A) Past residential exposure (in any period)	(B) Occupational and/or public exposure (everyday)	(A) or (B)
All never-smokers				
Number of cases	40	114	37	122
Person-years	50,662	127,309	35,258	134,299
RR[1] (95% CI)	1.00	1.1 (0.8 to 1.5)	1.3 (0.9 to 1.8)	1.2 (0.8 to 1.7)
RR[2] (95% CI)	1.00	1.0 (0.7 to 1.4)	1.3 (0.9 to 1.9)	1.1 (0.8 to 1.6)
Premenopausal women at baseline:				
No. of cases	9	61	28	68
Person-years	22,263	56,896	17,884	60,320
RR[1] (95% CI)	1.00	1.7 (1.0 to 3.0)	2.1 (1.3 to 3.4)	2.9 (1.4 to 5.8)
RR[2] (95% CI)	1.00	1.6 (0.9 to 2.7)	2.3 (1.4 to 3.8)	2.6 (1.3 to 5.2)
Postmenopausal women at baseline:				
Number of cases	31	51	8	52
Person-years	27,345	68,364	16,625	71,674
RR[1] (95% CI)	1.00	0.7 (0.4 to 1.1)	0.5 (0.3 to 1.1)	0.6 (0.4 to 1.0)
RR[2] (95% CI)	1.00	0.7 (0.4 to 1.1)	0.4 (0.2 to 1.0)	0.7 (0.4 to 1.0)

[1]Relative risks adjusted for public health center (4 areas) and age 4 5-year age group).– [2]Relative risks adjusted for public health center, age, employment status (employed and unemployed), education level (≥high school and <high school), body mass index (<22, 22 ≤<25 and ≥25), family history of breast cancer in mother or sisters, history of past benign breast disease, age at menarche, number of births (0 and ≥4), menopausal status (pre and post), hormone use and alcohol consumption per week (<once/week, <250 g/week and ≥250 g/week).

hormones admit of no doubt, and a causal model of breast cancer suggested that hormones increased the breast cancer risk in adults by increasing cell proliferation and the number of target cells, and also heightened the risk of the retention of spontaneous somatic mutations.[31] Therefore, higher levels of estrogens in premenopausal women may act jointly with exogenous carcinogens in breast carcinogenesis. The carcinogenic effects of tobacco smoke may result from a balance between its carcinogenic and anti-estrogenic effects.[6] Therefore, premenopausal women are likely to be affected by tobacco carcinogens because their estrogen levels are higher, thereby possibly canceling out the anti-estrogenic effects of tobacco smoke.

Smoking was reported to be associated with a decrease in the incidence of endometrial neoplasia in postmenopausal women.[23] The net effect of tobacco smoke may be antiestrogenic in the endometrium. However, available evidence, excluding 1 prospective study in Japan,[32] indicates that smoking has no beneficial effects in the breast. We did not observe statistically significant beneficial effects in the present study. However, our data suggest that at least the carcinogenic effects of tobacco smoke are not present in postmenopausal women.

Active and passive smoking are influenced by socioeconomic status.[33,34] Occupation is in fact related to smoking habits especially in women; working women generally smoke more and are exposed to sidestream smoke more frequently. Indeed, smoking status differed among several occupation-related factors in this cohort. A stratified analysis by employment status revealed interesting findings. In postmenopausal women, increased risk was observed only in employed women, although the small numbers of cases in the subgroup analyses precluded firm conclusions. Their pack-years were comparable (employed 10 ± 11 and unemployed 13 ± 13). These findings suggest that there were unknown residual confounders or different smoking behavior in these 2 groups. Risks for passive smoking were not increased in either employed or unemployed postmenopausal women. However, in premenopausal women, risks for active or passive smoking were increased in both employed and unemployed women. These findings suggest that any tobacco smoke exposure elevated the risk in premenopausal women no matter what their occupation. Educational level can be a surrogate indicator of socioeconomic status and has been reported as one of the important risk factors for breast cancer. Although we incorporated employment status and educational level into our statistical models, unknown residual confounders concerning socioeconomic status might not necessarily have been excluded from our analysis.

In our study, past exposure to sidestream smoke at home showed different effects from those by the occupational/social exposure. Residential exposure was defined as "a smoker(s) who had lived with a subject", although the current occupational/social exposure was assessed semi-quantitatively by self-report. Intensity or duration of daily exposure could not be estimated for the residential exposure. Previous cohort studies in Japanese women also used the smoking status of husbands as an index of passive smoking and did not observe elevated risk.[32,35]

The limitations of previous case-control studies were that recall and selection bias would tend to produce spurious positive association.[11] On the other hand, the limitations of previous cohort studies including misclassification of exposure and reference category have also been pointed out.[12–15] However, a well-designed prospective study is known to provide persuasive evidence. Our prospective study design also has some advantages in estimating the risks of smoking. Although recall bias may exist with information concerning passive smoking in a case-control study, there was no recall bias in our study because of its prospective nature. Never-active smokers without passive smoking were assigned to the reference, allowing for more accurate classification of exposure. Nonresidential passive smoking, *i.e.*, occupational or public exposure to tobacco smoke, was taken into account in the analyses. Subgroup analyses concerning menopausal status were done because the combined analyses may dilute the risk estimation.

On the other hand, there are some admitted limitations. Because the exposure assessment was done at 1 point (at baseline), a misclassification of the exposure might have occurred, thereby diluting the effects if some smoking women had quit smoking during the follow-up period. Information on the menopausal status was obtained at baseline. Therefore, we did not examine the risks for pre- and post-menopausal cancer. The relatively small number of incidence cases precluded further subgroup analyses. Results of the subgroup analyses according to menopausal status in this report should be confirmed by continued follow-up.

Different effects of active or passive smoking regarding breast cancer risk had been shown in premenopausal and postmenopausal women.[7,36] In a recent study, the risk of breast cancer among smokers has been clearly reported to be elevated in premenopausal women.[36] Immature breast cells are suggested to have especially increased susceptibility to smoking-related carcinogens.[6] In our

study, 94% of subjects had delivered children, but the effect of smoking in strata defined by age of full-term birth could not be examined. On the other hand, in postmenopausal women, the risk of breast cancer among smokers has been reported not to be elevated.[36] These previous observations are consistent with our observations regarding both active and passive smoking. Race is also an important factor in the interpretation of our results. To our knowledge, this is the first prospective study to link active smoking to breast cancer risk in Asian women, although recent large-scale cohort studies in America did not detect any increased risk of breast cancer.[10,11] Genetic differences concerning important metabolic enzymes, for example, higher frequency of a variant allele of cytochrome P450 1A1 gene, were reported,[37] and endogenous estrogen levels and the number of estrogen receptors have been reported to differ between Japanese and Caucasians.[38,39] Thus, an association between smoking and breast cancer might appear more readily in Japanese. The incidence of breast cancer among premenopausal women (88/90,161 person-year) was almost the same as that among postmenopausal women (90/107,241 person-year), and the association observed in premenopausal women was strong. These might be why we observed an elevated risk due to tobacco smoking in the overall subjects.

In conclusion, tobacco smoking increases the risk of female breast cancer in premenopausal women. Both active and passive smoking are promising targets in the prevention of breast cancer.

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Impact of alcohol drinking on total cancer risk: data from a large-scale population-based cohort study in Japan

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We conducted a cohort study of alcohol consumption and total cancer incidence and mortality in 73 281 subjects (35 007 men and 38 274 women) aged 40–59 years old at baseline over a 10-year follow-up period. During 1990–2001, a total of 3403 cases of newly diagnosed cancer and 1208 cancer deaths were identified. In men, the lowest risk of developing cancer was observed among occasional drinkers, and a linear positive association with increased ethanol intake was noted (hazard ratio 1.18 for 1–149 g per week, 1.17 for 150–299 g per week, 1.43 for 300–449 g per week, 1.61 for ⩾450 g per week, P for trend <0.001). The positive relation was similar for cancer incidence and mortality, but was more striking among current smokers and alcohol-related cancers. Relatively few women were regular drinkers. Our results suggest that increased ethanol intake linearly elevates the risk of cancer, and that nearly 13% of cancers among males in this study were due to heavy drinking (⩾300 g per week of ethanol), to which smoking substantially contributed. The simultaneous reduction of smoking is therefore important for reducing the effect of alcohol on cancer risk.

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In Japan, both alcohol consumption and the proportion of heavy drinkers have been increasing for decades (The Editorial Board of the Cancer Statistics in Japan, 2003), and alcohol drinking has been recognised as an important and preventable public health problem. A quantitative estimation of the effects of alcohol drinking in a target population, with regard to not only specific cancers but also total cancers, is important in formulating public health policies. However, evidence of the association between alcohol and total cancer risk mainly concerns Western populations and cancer mortality (Blackwelder *et al*, 1980; Blot, 1992; Doll *et al*, 1994; Fuchs *et al*, 1995; Camargo *et al*, 1997; Renaud *et al*, 1998; Berberian *et al*, 1994; Gaziano *et al*, 2000; Bagnardi *et al*, 2001; Theobald *et al*, 2001). Little has been reported for Japanese or other ethnic groups (Kono *et al*, 1986; Yuan *et al*, 1997, Tsugane *et al*, 1999).

As the epidemiological background, types of beverage regularly consumed and genetic polymorphisms for alcohol-related enzymes in these ethnic groups differ from those in Western populations, we have conducted a cohort analysis of the question using a large-scale population-based prospective study with a 10-year follow-up period.

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METHODS

Study population and baseline survey

The Japan Public Health Center-based prospective Study (JPHC Study) was launched in 1990 for Cohort I and in 1993 for Cohort II. Cohort I covered five prefectural public health center (PHC) areas and Cohort II covered six PHC areas. The details of the study design have been described elsewhere (Tsugane and Sobue, 2001). The study protocol was approved by the institutional review board of the National Cancer Center, Japan. In the present analysis, two PHC areas were excluded since different definitions of the study population had been applied.

The study population was defined as all registered Japanese inhabitants in the nine PHC areas aged 40–59 years at the start of each baseline survey. Initially, 96 616 subjects were identified but after excluding 178 subjects with non-Japanese nationality ($n=45$), late reports of emigration occurring before the start of the follow-up period ($n=131$), and incorrect birth date ($n=2$), a population-based cohort of 96 438 subjects (48 240 men and 48 198 women) was established.

A baseline self-administered questionnaire survey on various lifestyle factors was conducted in 1990 for Cohort I and in 1993–1994 for Cohort II, with a response rate of 81%. After excluding subjects with a self-reported serious illness (cancer, cerebrovascular disease, myocardial infarction, or chronic liver disease) and those without details of alcohol status, 73 281 subjects (35 007 men and 38 274 women) remained for analysis.

Information on alcohol intake was obtained in terms of frequency and the amount using validated questions (Otani *et al*,

2003; Tsubono *et al*, 2003). The average frequency was reported in six categories for cohort I: <1 day per month, 1–3 days per month, 1–2 days per week, 3–4 days per week, 5–6 days per week, and everyday. Subjects consuming alcoholic beverages at least once a week were also asked about the types of drinks consumed and the average consumption. Subjects in cohort II were also asked about their drinking status, never-, ex-, or current drinkers. Ex- and current drinkers provided information on the average frequency, the types of drinks consumed and average daily consumption. The average frequency of consumption was divided into the following categories, to each of which a score was assigned: 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, and 6 for 5–6 days per week and everyday in the cohort I questionnaire, and 1.5 for 1–2 days per week, 3.5 for 3–4 days per week, and 6 for almost everyday in the cohort II questionnaire. The amount of ethanol by type of beverage was calculated as follows: 180 ml of sake (rice wine) was regarded as 23 g of ethanol, 180 ml of shochu or awamori (white spirits) as 36 g, 633 ml of beer as 23 g, 30 ml of whiskey or brandy as 10 g, and 60 ml wine as 6 g. Finally, the weekly ethanol intake was estimated by multiplying the amount by the score. In the present analysis, alcohol drinking was classified into six categories: nondrinkers (<1 day per month), occasional drinkers (1–3 days per week), and four categories of regular drinkers (1–149, 150–299, 300–449, and ⩾450 g per week).

Follow-up and analysis

Subjects were followed from the baseline survey until December 31, 2001. Residence status, including survival, was confirmed annually through the residential registry kept in each municipality of the areas where the study subjects resided. Among the study subjects, 6.5% moved away and 0.06% were lost to follow-up during the study period. Information on the cause of each death was supplemented by checking against death certificate files with permission, and the cause of death was defined according to the International Classification of Disease, 10th Version (ICD-10) (WHO, 1990).

Cancers were identified by active patient notification from the local major hospitals in the study area and approved data linkage with the population-based cancer registries. Death certificates were used as a supplementary information source. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) (WHO, 2000). In 2.2% of cancer cases, information was available only from death certificates (DCO). The earliest date of diagnosis was used in cases with multiple primary cancers at different times.

Person-years were accrued from baseline survey until the following end points: for cancer incidence – the date of occurrence of cancer, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first; for total cancer deaths, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first. Persons who were lost to follow-up were censored at the last confirmed date of presence in the study area.

The study outcomes were defined as newly occurring cancers of any site and all cancer deaths during the study period. Hazard ratios (HR) and their 95% confidence intervals (95% CI) were used to describe the relative risk cancer deaths associated with the alcohol categories at baseline (nondrinkers, occasional drinkers, 1–149 g of ethanol per week, 150–299, 300–449, and ⩾450 g per week), with 'occasional drinkers' representing the reference category. In men, stratified analyses were further conducted to evaluate whether alcohol effects and cancer risk varied with smoking status. Interaction terms were generated by multiplying the ordinal smoking categories by ordinal alcohol drinking categories. The HRs were further estimated separately for alcohol-related cancers, namely cancer of the oral cavity, pharynx, larynx, oesophagus, and liver (IARC, 1988; WHO, 2003) (ICD-0-3: C00-C10, C12-C15, C22, C32), and for cancers not considered to be alcohol-related. The Cox proportional hazards model was used to control for such potential confounding factors as age at baseline

Table 1 Baseline characteristics of the study subjects according to alcohol drinking category

		Alcohol drinking category					
				Weekly ethanol intake (g per week)			
	Total	Nondrinkers	Occasional drinkers	1–149	150–299	300–449	⩾450
Men (n = 35 007)							
Number of subjects	35 007	7009	3555	7853	7039	4899	4652
Proportion (%)		20.0	10.2	22.4	20.1	14.0	13.3
Age (years) ±s.d.	49.1±5.9	49.8±6.0	48.6±5.9	48.7±6.0	49.0±5.9	49.4±5.8	49.1±5.9
Smoking status (%)							
Never	24.7	29.5	33.0	30.2	21.3	16.9	15.5
Former	21.1	19.8	19.0	22.7	21.9	21.6	20.1
Current	54.2	50.7	48.0	47.1	56.8	61.5	64.4
Green vegetable intake (%)							
Almost everyday	23.5	23.8	24.1	22.4	23.2	24.4	23.6
Leisure-time physical activity (%)							
⩾1–2 times per week	18.0	15.2	18.7	21.0	18.5	17.9	15.6
Women (n = 38 274)							
Number of subjects	38 274	29 356	4329	3584	593	191	221
Proportion (%)		76.7	11.3	9.4	1.5	0.5	0.6
Age (years) ±s.d.	49.4±5.9	49.8±5.9	47.8±5.7	48.0±5.6	47.9±5.7	47.2±5.4	47.3±5.5
Smoking status (%)							
Never	92.4	94.8	90.4	85.6	60.6	52.9	49.3
Former	1.4	1.0	2.1	2.4	6.3	6.8	3.6
Current	6.2	4.2	7.5	12.0	33.2	40.3	47.1
Green vegetable intake (%)							
Almost everyday	31.1	31.6	28.2	31.1	27.9	22.2	27.9
Leisure-time physical activity (%)							
⩾1–2 times per week	15.8	15.0	18.1	19.3	16.9	14.7	13.2

(continuous), study area (nine PHC areas), smoking status (pack-years (0, 1–19, 20–29, 30–39, ⩾40)), green vegetable intake (⩽3–4 times per week, everyday), and leisure-time physical activity (⩽1–3 times per month, ⩾1–2 times per week). These variables are either known or suspected risk factors for cancer or had been found to be associated with cancer risk in previous studies (Tsugane *et al*, 1999; Hara *et al*, 2002).

To express the impact of alcohol drinking on the risk of overall cancer, the population-attributable fraction (PAF) (%) was estimated as pd × (HR−1/HR), where pd is the proportion of cases exposed to the risk factors. This formula is considered more valid than the popular formula Pe × (RR−1)/(Pe × (RR−1) + 1), where Pe is the proportion of the source population exposed to the risk factor, when a confounding variable exists (Rockhill *et al*, 1998). Confidence intervals (95%) for the adjusted PAF were estimated using the formula of Greenland (1999). Stata version 8 special edition software (Stata Corporation, 2003) was used to perform the statistical analyses.

RESULTS

During the 721 302.5 person-years of follow-up (average: 9.8 years) for the 73 281 subjects (35 007 men and 38 274 women), a total of 3403 newly diagnosed cancers (1904 men and 1499 women) and 1208 cancer deaths (758 men and 450 women) were included in the analyses. With regard to cancer incidence, gastric cancer was the commonest cancer in men ($n = 533$, 28.0%), followed by colon ($n = 281$) and lung cancers ($n = 230$); in women, breast cancer was commonest ($n = 314$, 20.9%), followed by gastric cancer ($n = 203$), and colon cancers ($n = 170$). For mortality, lung cancer was the commonest cause of cancer death in men ($n = 167$, 22.0%), followed by gastric ($n = 148$) and liver cancer ($n = 74$); in women, gastric cancer was the commonest cause of cancer death ($n = 58$, 12.9%), followed by lung ($n = 56$), and breast cancer ($n = 40$).

At baseline, 70% of men were regular drinkers and 48% consumed alcohol 3–4 times per week or more; in women, 77% were nondrinkers and 12% regular drinkers. The average frequency of alcohol consumption among regular drinkers was 5.2 days per week in men and 3.6 days per week in women. Both in men and women (Table 1), the proportion of current smokers was increased in the higher ethanol intake groups, in which leisure-time physical activities were less frequent. However, no consistent trend in green vegetable intake was observed across the alcohol categories.

The adjusted cancer HRs by alcohol category are presented in Table 2, together with the ratios for cancer mortality. In men, the lowest risk was observed in occasional drinkers, compared to

Table 2 Hazard ratios (HR)[a] and 95% confidence interval (95% CI) of cancer incidence and deaths according to alcohol-drinking status

				Weekly ethanol intake (g per week)				
		Nondrinkers	Occasional drinkers	1–149	150–299	300–449	⩾450	*P* for trend
Men ($n = 35\,007$)								
Cancer incidence	Person-years	68 161.0	35 151.9	74 007.4	67 934.7	48 173.5	46 194.9	
Total ($n = 1904$)								
No. of cases		360	138	353	359	339	355	
HR (95% CI)		1.10 (0.90–1.34)	1.00 (reference)	1.18 (0.96–1.44)	1.17 (0.96–1.44)	1.43 (1.17–1.75)	1.61 (1.32–1.97)	<0.001
PAF% (95% CI)						5.4 (1.4–9.1)	7.1 (2.9–11.0)	
Excluding first 5 years ($n = 1172$)								
No. of cases		214	81	217	234	206	220	
HR (95% CI)		1.11 (0.86–1.44)	1.00 (reference)	1.25 (0.97–1.62)	1.29 (0.99–1.67)	1.44 (1.10–1.87)	1.64 (1.26–2.12)	0.002
PAF% (95% CI)						5.4 (0.3–10.2)	7.3 (1.9–12.4)	
Cancer deaths	Person-years	69 175.7	35 547.7	75 042.2	69 039.4	49 194.1	47 259.3	
Total ($n = 758$)								
No. of cases		161	59	138	119	133	148	
HR (95% CI)		1.10 (0.81–1.49)	1.00 (reference)	1.06 0.77–1.44)	0.92 (0.67–1.26)	1.33 (0.97–1.83)	1.58 (1.16–2.15)	<0.001
PAF% (95% CI)						4.4 (−1.7–10.1)	7.1 (0.4–13.4)	
Excluding first 5 years ($n = 533$)								
No. of cases		107	35	106	82	96	107	
HR (95% CI)		1.25 (0.85–1.85)	1.00 (reference)	1.39 (0.94–2.06)	1.08 (0.72–1.62)	1.62 (1.09–2.42)	1.90 (1.28–2.81)	0.009
PAF% (95% CI)						6.9 (−1.1–14.3)	9.5 (0.6–17.6)	
Women ($n = 38\,274$)								
Cancer incidence	Person-years	293 866.0	43 116.9	34 966.7	5757.5	1803.8	2168.2	
Total ($n = 1499$)								
No. of cases		1170	178	118	20	6	7	
HR (95% CI)		0.94 (0.80–1.11)	1.00 (reference)	0.80 (0.63–1.01)	0.68 (0.42–1.11)	0.73 (0.32–1.66)	0.68 (0.32–1.46)	0.659
Excluding first 5 years ($n = 908$)								
No. of cases		707	115	68	12	3	3	
HR (95% CI)		0.88 (0.72–1.08)	1.00 (reference)	0.70 (0.51–0.95)	0.59 (0.31–1.13)	0.59 (0.19–1.88)	0.47 (0.15–1.49)	0.351
Cancer deaths	Person-years	298 259.9	43 775.0	35 434.0	5827.6	1821.6	2187.6	
Total ($n = 450$)								
No. of cases		368	43	28	6	3	2	
HR (95% CI)		1.08 (0.79–1.49)	1.00 (reference)	0.79 (0.49–1.27)	0.54 (0.19–1.52)	1.27 (0.39–4.15)	0.68 (0.16–2.86)	0.896
Excluding first 5 years ($n = 325$)								
No. of cases		273	31	17	3	1	0	
HR (95% CI)		1.14 (0.78–1.66)	1.00 (reference)	0.69 (0.38–1.25)	0.20 (0.03–1.51)	0.69 (0.09–5.09)	—	0.289

[a]Adjusted for age at baseline (continuous), study area (9 PHC area), pack-years of smoking (0, 1–19, 20–29, 30–39, ⩾40), green vegetable intake (⩽3–4 times per week, almost everyday), and leisure-time physical activity (⩽1–3 times per month, ⩾1–2 times per week).

whom a significant increase in risks of cancer occurrence was observed as ethanol intake increased among regular drinkers (1–149 g per week: HR = 1.18, 150–299 g per week: HR = 1.17, 300–449 g per week: HR = 1.43, ⩾450 g per week: HR = 1.61, *P* for trend <0.001). This trend did not change when cases where the cancers occurred within the first five years of the study were excluded. For total cancer mortality, a similar trend was observed. Among males, 12.5% of the cancers in the study period were attributable to heavy drinking (⩾300 g of ethanol per week): 5.4% for the consumption of 300–449 g of ethanol per week and 7.1% for the consumption of ⩾450 g per week. Similar results were obtained for cancer mortality. Unlike men, cancer risk was the

Table 3 Hazard ratios (HR)[a] and 95% confidence interval (95% CI) of cancer incidence and deaths attributed to alcohol-related cancers and nonalcohol-related cancers[b] according to the alcohol drinking status in men (*n* = 35 007)

			Weekly ethanol intake (g per week)					
	Nondrinkers	**Occasional drinkers**	**1–149**	**150–299**	**300–449**	**⩾450**	***P* for trend**	***P* for interaction**
Cancer incidence								
Never-smokers (n = 315)								
No. of cases	78	42	75	54	37	30		
HR (95% CI)	0.90 (0.62–1.31)	1.00 (reference)	0.87 (0.60–1.28)	0.86 (0.57–1.29)	1.03 (0.66–1.62)	1.02 (0.64–1.64)	0.370	
Current smokers (n = 1163)								0.018
No. of cases	196	58	202	226	224	257		
HR (95% CI)	1.39 (1.03–1.88)	1.00 (reference)	1.69 (1.25–2.28)	1.64 (1.22–2.20)	1.93 (1.43–2.60)	2.32 (1.72–3.11)	<0.001	
Alcohol-related cancers (*n* = 250)								
No. of cases	29	8	38	49	52	74		
HR (95% CI)	1.57 (0.72–3.45)	1.00 (reference)	2.28 (1.06–4.90)	2.95 (1.39–6.28)	4.03 (1.90–8.56)	6.16 (2.95–12.8)	<0.001	
Never smokers (n = 34)								
No. of cases	7	2	8	5	6	6		
HR (95% CI)	1.88 (0.39–9.09)	1.00 (reference)	2.09 (0.44–9.95)	1.91 (0.37–9.95)	3.42 (0.65–17.9)	4.70 (0.93–23.7)	0.109	
Current smokers (n = 163)								
No. of cases	14	5	19	36	33	56		
HR (95% CI)	1.12 (0.40–3.15)	1.00 (reference)	1.95 (0.73–5.24)	3.23 (1.26–8.28)	3.72 (1.44–9.62)	6.41 (2.55–16.1)	<0.001	
Nonalcohol-related cancers (*n* = 1654)								
No. of cases	331	130	315	310	287	281		
HR (95% CI)	1.07 (0.87–1.31)	1.00 (reference)	1.11 (0.90–1.36)	1.06 (0.86–1.31)	1.27 (1.03–1.57)	1.34 (1.11–1.66)	0.004	
Never smokers (n = 282)								
No. of cases	71	40	67	49	31	24		
HR (95% CI)	0.85 (0.57–1.26)	1.00 (reference)	0.81 (0.55–1.20)	0.80 (0.53–1.23)	0.92 (0.57–1.48)	0.85 (0.51–1.42)	0.733	
Current smokers (n = 1000)								
No. of cases	182	53	183	190	191	201		
HR (95% CI)	1.41 (1.03–1.93)	1.00 (reference)	1.66 (1.21–2.27)	1.48 (1.08–2.03)	1.76 (1.28–2.41)	1.94 (1.42–2.66)	0.039	
Cancer deaths								
Never-smokers (n = 124)								
No. of cases	36	25	27	19	7	10		
HR (95% CI)	0.67 (0.40–1.12)	1.00 (reference)	0.53 (0.31–0.92)	0.49 (0.27–0.91)	0.33 (0.14–0.78)	0.55 (0.26–1.16)	0.634	
Current smokers (n = 484)								<0.001
No. of cases	81	23	83	84	99	114		
HR (95% CI)	1.43 (0.89–2.31)	1.00 (reference)	1.68 (1.04–2.69)	1.52 (0.94–2.44)	2.15 (1.35–3.44)	2.57 (1.62–4.09)	<0.001	
Alcohol-related cancers (*n* = 143)								
No. of cases	19	5	25	28	31	35		
HR (95% CI)	1.58 (0.59–4.25)	1.00 (reference)	2.26 (0.86–5.92)	2.55 (0.98–6.67)	3.86 (1.48–10.0)	4.89 (1.90–12.5)	0.003	
Never smokers (n = 22)								
No. of cases	7	2	4	4	2	3		
HR (95% CI)	1.76 (0.36–8.54)	1.00 (reference)	1.01 (0.18–5.59)	1.45 (0.26–8.04)	1.29 (0.18–9.37)	2.35 (0.38–14.4)	0.280	
Current smokers (n = 89)								
No. of cases	6	3	14	20	20	26		
HR (95% CI)	0.81 (0.20–3.26)	1.00 (reference)	2.17 (0.62–7.57)	2.66 (0.78–9.07)	3.45 (1.01–11.8)	4.78 (1.43–15.9)	0.014	
Nonalcohol-related cancers (*n* = 615)								
No. of cases	142	54	113	91	102	113		
HR (95% CI)	1.06 (0.77–1.45)	1.00 (reference)	0.94 (0.68–1.31)	0.76 (0.54–1.08)	1.09 (0.78–1.53)	1.27 (0.91–1.77)	0.010	
Never smokers (n = 102)								
No. of cases	29	23	23	15	5	7		
HR (95% CI)	0.57 (0.33–1.00)	1.00 (reference)	0.49 (0.27–0.88)	0.41 (0.21–0.80)	0.26 (0.10–0.68)	0.41 (0.17–0.96)	0.287	
Current smokers (n = 395)								
No. of cases	75	20	69	64	79	88		
HR (95% CI)	1.53 (0.92–2.54)	1.00 (reference)	1.60 (0.96–2.67)	1.34 (0.80–2.25)	1.96 (1.18–3.25)	2.25 (1.36–3.72)	0.008	

[a]Adjusted for age at baseline (continuous), study area (9 PHC area), daily cigarette consumption (number of cigarettes, continuous, current smoker only), green vegetable intake (⩽3–4 times per week, almost everyday), and leisure-time physical activity (⩽1–3 times per month, ⩾1–2 times per week). [b]Alcohol-related cancers consist of cancer of the oral cavity, pharynx, oesophagus, liver, and larynx. Nonalcohol-related cancers consist of all other cancers not considered to be alcohol related.

highest among occasional drinkers in women, but none of the risk values reached statistical significance.

The HRs for cancer in men were estimated separately by smoking status at baseline for each alcohol-drinking category (Table 3). For cancer incidence, no risk fluctuation was observed among never-smokers, whereas current smokers exhibited a constantly elevated risk compared with occasional drinkers (1–149 g per week: HR = 1.69, 150–299 g per week: HR = 1.64, 300–449 g per week: HR = 1.93, ⩾450 g per week: HR = 2.32, P for trend <0.001). Similar trends were observed for cancer mortality, with a somewhat decreased risk tendency among never-smokers. A statistically significant interaction between alcohol and smoking status applied to the risks of both total cancer incidence ($P=0.018$) and mortality ($P<0.001$).

The HRs for cancer in men were also separately determined for alcohol-related and other cancers (Table 3). As expected, increased risks were more evident for alcohol-related cancers than those for other cancers. In a further analysis restricted to alcohol-related cancers by smoking status, increased risks for the high-alcohol categories were also observed among never smokers, though less than among current smokers.

DISCUSSION

In this cohort study, the lowest risk of cancer was observed among male occasional drinkers, and a linear positive association with increasing ethanol intake was seen, with up to a 61% excess cancer risk among subjects with an ethanol intake of ⩾450 g. The positive association was similar for both the cancer incidence and mortality, but was more striking among current smokers and for alcohol-related cancers. Considerable interaction between smoking and alcohol drinking was observed. On the other hand, no clear association between alcohol drinking and cancer was found in women, probably because few of them were regular drinkers. Among males, nearly 13% of the cancers were considered attributable to heavy drinking (⩾300 g of ethanol per week).

We assigned occasional drinkers to the reference category since nondrinkers were a mixture of never- and ex-drinkers, both of which contained subjects who are unable to drink due to a deficiency in the key enzyme for alcohol metabolism, common in the Japanese population. This might have complicated the interpretation of the results for nondrinkers. We were unable to assess the risk of never- and ex-drinkers separately, since the baseline questionnaire for cohort I did not discriminate abstainers from nondrinkers. Additional analyses using cohort II subjects, however, found that only 2% of all male subjects were ex-drinkers, and also no marked difference in the association among nondrinkers whether ex-drinkers were included or excluded. If this was also the case in cohort I, it seems unlikely that 'never-drinking' would be associated with an increased risk of cancer, though the possible residual confounding effects cannot be ruled out. Approximately half of the Japanese individuals were found to have a deficient phenotype for aldehyde dehydrogenase-2, a key enzyme in the conversion of acetaldehyde to acetate (Agarwal *et al*, 1981; Shibuya and Yoshida, 1988), resulting in higher levels of acetaldehyde exposure, which is considered to be carcinogenic (IARC, 1988). The fraction of cancer risk attributable to alcohol might therefore be greater among Japanese than among Western drinkers.

Previous studies have indicated that the effect of alcohol drinking does not appear to be due to any specific type of alcoholic beverage, but rather due to ethanol itself. In our study, most male regular drinkers drank two or more types of alcohol; 36% of the total ethanol intake among these subjects was from Japanese sake (rice wine), 33% from Japanese hard liquor, 24% from beer and 7% from whisky, whereas <1% was from wine and other alcoholic beverages.

Our results indicate that the combination of alcohol drinking and smoking is associated with a particularly increased risk of cancer and presumably makes a major contribution to both incidence and mortality of the overall cancer risk, while no such tendency was detected among never-smokers. Except for our previous work, studies of the effect of interaction between drinking and smoking on the total cancer risk in the Japanese are sparse (Tsugane *et al*, 1999; Hara *et al*, 2002). CYP2E1, the expression of which is induced by alcohol, metabolises procarcinogens, such as *N*-nitroso compounds, present in tobacco smoke and foods (Anderson *et al*, 1994); it also catalyses the conversion of alcohol to acetaldehyde. Animal experiments have suggested that carcinogens in tobacco smoke are metabolised more slowly among drinkers (Van de Wiel *et al*, 1993; Anderson *et al*, 1994). Although interaction between alcohol and smoking may greatly contribute to the risk of both cancer incidence and mortality, alcohol may also be an independent risk factor, at least for alcohol-related cancers.

The major strengths of our study were its prospective design, its high response rate, and the negligible proportion of losses to follow-up. The collection of alcohol details before cancer diagnosis precluded the exposure recall bias inherent in case–control studies. However, misclassification of the self-reported alcohol due to modified alcohol-drinking behaviour during the study period is possible. However, these would probably be nondifferential and may underestimate the true relative risk. Although the quality of the cancer registry system was satisfactory during the study period, there was some geographical variation by study area, so this was adjusted for in the analysis. We also confirmed that the quality of the registry was not affected by drinking status at baseline, so underreporting of cancer should also have been nondifferential.

Our cohort study found that an increased ethanol intake substantially elevates the risk of total cancer, but this effect appeared to be largely due to interactions with smoking. For cancer prevention therefore, combined cessation of smoking and alcohol drinking is important for the reduction of cancer risk.

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Appendix

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Influence of Coffee Drinking on Subsequent Risk of Hepatocellular Carcinoma: A Prospective Study in Japan

Manami Inoue, Itsuro Yoshimi, Tomotaka Sobue, Shoichiro Tsugane

For the JPHC Study Group

Background: **An association between coffee drinking and reduced risk of liver cancer has been suggested by animal studies, but epidemiologic evidence of such an association in a high-risk population is lacking. We conducted a large-scale population-based cohort study of the association between coffee drinking and hepatocellular carcinoma (HCC) in a Japanese population.** ***Methods:*** **Newly diagnosed case patients (250 men and 84 women) with HCC were identified from a 10-year follow-up of the Japan Public Health Center-based Prospective Study, which consists of 90 452 middle-aged and elderly Japanese subjects (43 109 men and 47 343 women). Case patients were grouped according to coffee intake and were stratified by hepatitis virus infection, sex, age, diet, lifestyle factors, and previous history of liver disease. Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CIs) for HCC were calculated with Cox proportional-hazards modeling. All statistical tests were two-sided.** ***Results:*** **Subjects (men and women combined) who consumed coffee on a daily or almost daily basis had a lower HCC risk than those who almost never drank coffee (HR = 0.49 [95% CI = 0.36 to 0.66]); risk decreased with the amount of coffee consumed (compared with nondrinkers, the HR for 1–2 cups per day = 0.52 [95% CI = 0.38 to 0.73]; for 3–4 cups per day = 0.48 [95% CI = 0.28 to 0.83]; for ≥5 cups per day = 0.24 [95% CI = 0.08 to 0.77], $P_{trend} < .001$). The risk of liver cancer in almost never drinkers in this population was 547.2 cases per 100 000 people over 10 years, but it was 214.6 cases per 100 000 people with drinking coffee on a daily basis. The inverse association persisted when the participants were stratified by lifestyle factors. Similar associations were observed when the analysis was restricted to hepatitis C virus-positive patients (all daily drinkers compared with nondrinkers: HR = 0.57 [95% CI = 0.37 to 0.86]), to hepatitis B virus-positive patients (HR = 0.60 [95% CI = 0.31 to 1.18]) and to subjects with no past history of chronic liver disease (HR = 0.45 [95% CI = 0.30 to 0.67]).** ***Conclusions:*** **In the Japanese population, habitual coffee drinking may be associated with reduced risk of HCC. [J Natl Cancer Inst 2005;97:293–300]**

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and is characterized by international variation in its distribution *(1)*; these variations are related to the distribution of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection. Chronic infection with HCV or HBV has been established as a major risk factor for HCC *(2)*. Other possible risk factors for HCC have been identified, but only a few factors, such as excess alcohol consumption, which leads to liver cirrhosis, and food contamination with aflatoxin, have been recognized as important; other modifiable factors have yet to be established *(3)*.

Coffee is consumed in many parts of the world, and a wide variety of drinking habits has been documented *(4)*. Coffee drinking was introduced to Japan 200 years ago, and coffee has since become a popular beverage. Japanese individuals reportedly drink an average 10 cups of coffee per week, 63% of which is consumed at home. Instant coffee and regular roasted coffee are the major types of coffee consumed in Japan *(5)*. The potential beneficial health effects of coffee consumption have been recognized for years; coffee is known to contain a high level of anticancer compounds, such as chlorogenic acids, and animal experiments have demonstrated an inhibitory effect of coffee on liver carcinogenesis *(6)*. Epidemiologic investigation of the association between coffee drinking and HCC, however, has been limited to several case–control studies targeting high-risk populations in Southern Europe *(7–9)*, in which an inverse association between coffee drinking and HCC was observed. However, prospective analyses and reports on other high-risk populations, such as Asian populations, are lacking.

Liver cancer is one of the major forms of cancer in Japan. HCC accounts for 90% of all cases of liver cancer diagnosed in Japan, and persistent HCV or HBV infections have been identified as causative factors in 80 and 10% of all Japanese liver cancer patients, respectively *(10)*. HCV infection in Japan is thought to have originated at the end of the 19th century, and it became widely disseminated in the 1930s and 1940s *(11)*. HCC prevention among HCV carriers has recently been improved to some degree as a result of interferon therapy *(12)*. However, from a public health point of view, environmental risk modifiers for the development of HCC that are effective in all patients, even those with hepatitis virus, must be explored.

Epidemiologic studies on Japanese immigrants in Brazil have shown a drastic decrease in the rates of mortality from liver cancer *(13)* and chronic liver disease *(14)*, without apparent change in the prevalence of HBV infection *(13)*. These reports suggest that changes in the environmental factors of the host country may act to prevent chronic liver disease and liver cancer; the introduction of coffee-drinking habits after immigration is one conceivable candidate. In the present study, we attempted to determine whether an association between coffee drinking and HCC exists in the Japanese population by carrying out a prospective analysis of data from a large-scale population-based cohort study in Japan.

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See "Notes" following "References."

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Subjects and Methods

Study Population

The Japan Public Health Center-based Prospective Study (JPHC Study) was launched in 1990 when Cohort I was established. Cohort II was added in 1993. Cohort I included five prefectural public health center areas: Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture), and Katsushika (metropolitan Tokyo), and cohort II included six prefectural public health center areas: Mito (Ibaraki Prefecture), Kashiwazaki (Nigata Prefecture), Chuohigashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture), and Suita (Osaka Prefecture). The details of the study design have been described elsewhere *(15)*. The study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan. The Katsushika and Suita public health center areas were excluded from the analysis because different definitions of the study population were used in these areas. Only people 40 and 50 years of age at baseline were invited to participate in these two areas, which may have limited the generalizability.

The study population was defined as all registered Japanese inhabitants in the nine public health center areas, who were between the ages of 40 and 59 years (Cohort I) and between the ages of 40 and 69 years (Cohort II) at the beginning of each baseline survey. The Japanese inhabitants were identified using population registries maintained by local municipalities. A total of 116 896 subjects were initially identified. During the follow-up period, 210 subjects were found to be ineligible for the study and were excluded because of non-Japanese nationality (n = 51), late reports of emigration occurring before the start of the follow-up period (n = 156), and ineligibility because of an incorrect birth date (n = 3). As a result, a population-based cohort of 116 686 subjects (57 583 men and 59 103 women) was established.

A baseline self-administered questionnaire on various lifestyle factors was given to participants in 1990 (Cohort I) and in 1993 and 1994 (Cohort II). A total of 95 376 subjects responded to the questionnaire, for a response rate of 82%. The questionnaire contained items on demographic characteristics; medical history (including a specific question on cirrhosis and hepatitis); family history; smoking and alcohol-, tea-, and coffee-drinking habits; dietary habits; other lifestyle factors, such as physical activity, bathing, and sleeping habits; bowel habits; and personality. Information on coffee drinking was obtained in terms of frequency and amount of coffee intake and divided into the following categories: almost never, 1–2 days per week, 3–4 days per week, and almost daily (further divided into 1–2 cups/day, 3–4 cups per day, or ≥5 cups per day). The type of coffee consumed (decaffeinated or caffeinated) was not included in the questionnaire. However, decaffeinated coffee is rarely consumed in Japan.

Subjects were followed from the date of the baseline survey through December 31, 2001. Residence status and survival were confirmed annually using the residential registers kept by each municipality in each of the study areas or, for those who had moved out of the study area, through the municipal office of the area to which they had moved. Inspection of the resident register is open to the general public under the resident registration law. In Japan, residency and death registration is required by law, and the registries are believed to be complete. Information on the cause of death was obtained by examining the death certificate provided by the Ministry of Health, Labor, and Welfare after the Ministry of Internal Affairs and Communications granted permission. Among the study subjects, 4890 died, 5211 moved out of the study area, and 47 were lost to follow-up during the follow-up period.

The occurrence of cancer was identified by active patient notification by the local major hospitals in the study area and data linkage with the population-based cancer registries with permission from each of the local governments responsible for the cancer registries. Death certificate information was used as a supplementary information source. The site and histology of each cancer were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) *(16)*. In the cancer registry system used in this study, the proportion of patients with incident cancers who first came to the attention of the cancer registry via a death certificate (death certificate notifications, or DCNs) was 8.5%, and the proportion of case patients for which information regarding cancer diagnosis was available only from death certificates (death certificate only, DCO) was 2.3% during the study period. These results were considered to be of adequate quality and completeness for the present study. Among the 361 incident liver cancers identified (ICD-O-3: C22), a total of 334 cases of newly diagnosed HCC (ICD-O-3: C22.0, 817) were identified as of December 31, 2001, after excluding 27 cases (7.5%) of liver cholangiocarcinoma (ICD-O-3: C22.1, 816). Information on hepatitis virus infection status of the case patients was obtained from the medical institutions where the case patients had been diagnosed if infection markers, such as antibodies to HCV (anti-HCV) or hepatitis B surface antigen (HbsAg), had been detected. In the present study, case patients who had been identified with anti-HCV antibodies were considered to be HCV positive, and those identified with HbsAg were considered to be HBV positive. Subjects with a present or past history of self-reported serious illness at baseline (cancer, cardiovascular disease, or myocardial infarction) were excluded from the analysis (n = 3799). After exclusion of 1125 subjects for whom the information on coffee intake was incomplete, 90 452 subjects, including 334 incident HCC case patients, were used in the analysis.

The person-years of follow-up were counted from the baseline survey until the date of HCC diagnosis, migration out of the study area, death, or the end of the study period (December 31, 2001), whichever came first. Persons lost to follow-up were censored on the last confirmed date of their presence in the study area.

Statistical Analysis

Outcome was defined as the new development of a primary HCC during the study period. Hazard ratios (HR) and their 95% confidence intervals (95% CI) were calculated using Cox proportional-hazards models and were used to describe the relative risks of HCC that were associated with the coffee-drinking categories at baseline. Differences in characteristics between categories of coffee intake were evaluated by analysis of variance and chi-square test for homogeneity. Models were adjusted for potential confounding factors, including age at baseline (3-year age categories), study area (nine public health center areas), and in additional analysis, smoking status (never, former, current), ethanol intake (non- and ex-drinkers, less than weekly, weekly or more [<150 g per week or ≥150 g per week]), green vegetable intake (<3 times per week, 3–4 times per week, everyday) and