研究成果の刊行に関する一覧表

雑誌

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Machida-Montani A, Tsugane S, 他	Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan.	Gastric Cancer	7	46-53	2004
Kim MK, Tsugane S, 他	Prospective study of three major dietary patterns and risk of gastric cancer in Japan.	Int J Cancer	110	435-442	2004
Inoue M, Tsugane S, 他	Impact of tobacco smoking on subsequent cancer risk among middle-aged Japanese men and women: data from a large-scale population-based cohort study in Japan -The JPHC Study.	Prev Med	38	516-522	2004
Liu Y, Tsugane S, 他	Vegetable, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study.	Cancer Causes Control	15	349-357	2004
Sasazuki S, Tsugane S, 他	Green tea consumption and susequent risk of gastric cancer by subsite: the JPHC Study.	Cancer Causes Control	15	483-491.	2004
Inoue M, Tsugane S, 他	Impact of body mass index on the risk of total cancer incidence and mortality among middle-aged Japanese: data from a large-scale population-based cohort study -The JPHC Study.	Cancer Causes Control	15	671-680	2004
Kobayashi M, Tsugane S, 他	Fish, Long-Chain n-3 Polyunsaturated Fatty Acids, and Risk of Colorectal Cancer in Middle-Aged Japanese: The JPHC Study.	Nut Cancer	49	323-40	2004
Mizoue T, 他	Ecological study of solar radiation and cancer mortality in Japan.	Health Phys	87	532-538	2004
Mizoue T, 他	Dietary pattern and colorectal adenomas in Japanese men: The Self-Defense Forces Health Study.	Am J Epidemiol	161	338-345	2005

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Original article

Association of *Helicobacter pylori* infection and environmental factors in non-cardia gastric cancer in Japan

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Abstract

Background. **Although *Helicobacter pylori* infection is a major risk factor for gastric cancer, it does not explain the full picture of stomach carcinogenesis. There have been few epidemiological studies, however, which examined both *H. pylori* and environmental factors simultaneously. The aims of this study were to estimate the association of environmental factors (smoking and dietary factors) with gastric cancer in consideration of *H. pylori* infection, and to investigate the effects of the interaction between environmental factors and *H. pylori* infection.**

Methods. **A multicenter, hospital-based, case-control study of gastric cancer was conducted at four hospitals in Nagano prefecture, Japan, between October 1998 and March 2002. For 153 newly diagnosed gastric cancer cases, two controls matched by age (within 3 years), sex, and residence area were randomly selected from the participants of a health check-up program during the same period in the same hospitals. We conducted a questionnaire survey and obtained blood samples. Consequently, 122 non-cardia gastric cancer cases and 235 controls were available for this analysis.**

Results. ***H. pylori*** **infection was strongly associated with non-cardia gastric cancer after adjustment for possible confounding factors (odds ratio [OR], 8.2; 95% confidence interval [CI], 3.7–18.2). Cigarette smoking (OR, 2.8; 95% CI, 1.2–6.5) and frequent intake of miso (fermented soy bean) soup (OR, 2.1; 95% CI, 0.9–5.1) and rice (OR, 2.5; 95% CI, 1.0–6.1) were determined to be risk factors even after adjusting for possible confounding factors, including *H. pylori* infection. However, no statistically significant interaction between environmental factors and *H. pylori* infection was detected.**

Conclusion. **This finding suggests that although *H. pylori* infection is clearly an important risk factor for gastric cancer, smoking cessation and dietary modification may be practical strategies for the prevention of non-cardia gastric cancer among both *H. pylori*-positive and -negative subjects in Japan.**

Key words *Helicobacter pylori* · Gastric cancer · Smoking · Diet · Case-control study

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Introduction

In 1994, the International Agency for Research on Cancer recognized *Helicobacter pylori* as a class I human carcinogen. A combined analysis of 12 case-control studies nested within prospective cohorts suggested that the odds ratio (OR) for the association between *H. pylori* infection and gastric cancer was 2.36 (95% confidence intervals [CIs], 1.98–2.81) [1]. Thus, there is a strong link between *H. pylori* and gastric cancer in many countries. By contrast, low gastric cancer rates have been reported in some countries with a high prevalence of *H. pylori* infection, such as India and Bangladesh [2]. This difference in gastric cancer rates in populations with similar high prevalences of *H. pylori* infection could be related to the difference in the diversity of *H. pylori* strains, ethnicity, and environmental factors.

There is recently increasing evidence that *H. pylori* strains that possess the cytotoxin-associated gene A (CagA) are associated with an increased risk of atrophic gastritis and gastric cancer. CagA-positive *H. pylori* infection strongly increased the risk for gastric cancer compared with *H. pylori*-uninfected subjects [3–6].

In a case-control study in Brazil, Tatemichi et al. [7] showed there were ethnic differences in the strength of the association between CagA serological status and non-cardia gastric cancer, which suggested that environmental factors played an important role in gastric car-

cinogenesis in Japanese Brazilians compared to non-Japanese Brazilians.

A relationship between environmental factors and gastric cancer has been reported in numerous previous studies [8–12]. A low intake of vegetables and a high intake of salt and salty foods were considered to be risk factors for gastric cancer [10,11]. Our previous study showed the protective effect of mushrooms and cruciferous vegetables among the same subjects as those of this present study, although we did not take into account *H. pylori* infection [12]. Moreover, there have been few epidemiological studies that have investigated the association between environmental factors and gastric cancer in consideration of *H. pylori* infection, and the interaction between environmental factors and *H. pylori* infection [13–16].

Concerning anatomical subsites, gastric cancer has been divided into two groups: "cardia" cancer (the upper third around the cardia) and "non-cardia" cancer (middle body and antrum). In the study by Hansen et al. [17], *H. pylori* infection was found to be associated with an increased risk of non-cardia cancer, but had an inverse association with cardia cancer. Our study subjects were restricted to cases of non-cardia cancer, which had a strong association with *H. pylori* infection.

The aim of this study was not only to confirm the association between non-cardia gastric cancer and *H. pylori* infection, combined with CagA, but also to estimate the association of environmental factors (smoking and dietary factors) with non-cardia cancer in consideration of *H. pylori* infection, which is a prevalent risk factor. We also investigated the effects of the interaction between environmental factors and *H. pylori* infection.

Subjects and methods

Subjects

A multicenter, hospital-based, case-control study of stomach cancer was conducted at four hospitals in Nagano prefecture, Japan, between October 1998 and March 2002. One hundred and fifty-three incident cases (in patients aged 20 to 74 years), of gastric cancer with histologic confirmation were newly diagnosed at these hospitals. For the 153 gastric cancer cases identified, two controls matched by age (within 3 years), sex, and residence area were randomly selected from the participants of a health check-up program during the same period in the same hospitals; they were confirmed to be cancer-free and with no past history of cancer. We conducted a questionnaire survey and obtained blood samples, with signed informed consent, from the 153 cancer-case patients and the 301 control subjects, before treatment for gastric cancer. Of the 153 gastric cancer cases, cardia cancer cases (in the upper third around the cardia), cases with uninformative anatomical subsite, and their control subjects were excluded from this study. A total of 126 non-cardia gastric cancer cases (middle body and antrum) and 247 controls remained. We also excluded subjects with extreme caloric intake (for men, <500 or ≥4000 kcal/day; for women, <400 or ≥3500 kcal/day), because this information was unreliable. Consequently, 122 non-cardia cancer cases and 235 controls were available for this analysis.

Questionnaire

The questionnaire was composed of items such as general characteristics (age, sex, sociodemographic characteristics), personal medical history, family history, smoking and drinking history, supplement use, and dietary factors. We also asked whether they were members of the Japan Agricultural Cooperatives (JA), because JA members may have particular dietary habits. JA members, who were farmers, were more familiar with health check-up programs than non-members. Therefore, we performed a careful multivariate adjustment for confounding factors, including JA membership, in order to exclude the effects of these factors.

All subjects were asked about the average frequency of intake and portion size of 141 items in the year preceding the interview or before a change of dietary habit, if the change had occurred in the past year. If they had any symptoms, their habitual intake prior to the symptoms was elicited. Daily consumption of rice and miso soup was classified into nine categories (<1, 1, 2, 3, 4, 5, 6, 7–9, 10+ cups/day). The frequency of other food items was classified into nine categories (never, 1–3 times/month, 1–2, 3–4, or 5–6 times/week, almost once/day, 2–3, 4–6 or >7 times/day), and the portion size was classified into three categories (more than 1.5 portions, same as the usual portion size, or less than half a portion). The mean daily consumption of each food group was calculated by multiplying the frequency and portion size. The estimated intake calculated by the questionnaire had been validated against a 14- or 28-day dietary record in a prior study. The Spearman correlation coefficients for intake of total vegetables, total fruits, pickled vegetables, and sodium were 0.36, 0.61, 0.74, and 0.59 in males and 0.34, 0.50, 0.75, and 0.55 in females, respectively [18,19].

Laboratory data

The study subjects were tested for serum pepsinogen I (PG I) and pepsinogen II (PG II), and for IgG antibody to *H. pylori* (Hp-Ab) and CagA (CagA-Ab). These antibodies were measured with an enzyme-linked

immunosorbent assay (ELISA; Helico G; Porton-Cambridge, Oxford, UK) kit and CagA kit (RADIM, Rome, Italy). Equal to and more than ten units per milliliter (U/ml) were considered a positive test in both Hp-Ab and CagA-Ab. *H. pylori* infection was defined when one or both serum assays were positive. The serum PG I and PG II levels were measured by radioimmunometric assay kits (PG1/PG2 RIABEAD; Dainabot, Tokyo, Japan). Atrophic gastritis was diagnosed according to the criteria of a PG I level below 70ng/ml and a PG I/PG II ratio below 3.0. The prevalence of serologically diagnosed atrophic gastritis using these criteria was well correlated ($r = 0.999$; $P < 0.0001$) with the age-adjusted mortality rate of gastric cancer among five Japanese populations [20].

To estimate the association between environmental factors and non-cardia cancer, the total intake of each food group and the frequency of each food item were each divided into three categories, at the nearest tertile based on the distribution in the control group. Smoking status was classified as never, past, or current smoker. The linear trend was assessed by assigning ordinal values for categorical factors.

In order to estimate the joint effects of environmental factors and *H. pylori* infection, the total consumption of vegetables, fruits, and salt was classified into a high-intake (above median intake) or a low-intake group (below median intake) according to the distribution of the control group. The number of cups per day was classified in two categories (high and low intake) for miso soup and rice. Smoking status was classified into two groups: never smoker and ever (past or current) smoker. We assessed the association with non-cardia cancer by taking into consideration the patterns of joint occurrence of both factors (environmental factors and *H. pylori* infection). Furthermore, the effect of interaction was checked by calculating an interaction term, and multiplying a dummy variable for each environmental factor by one for *H. pylori* infection.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) and trends were obtained by conditional logistic regression analysis. All P values were two-sided and all the statistical analysis was performed using the SAS statistical software package [21].

Results

The mean ages of cases and controls were 57.8 and 57.4 years, respectively. The proportion of male participants was 67.2% in cases and 67.7% in controls.

Table 1 shows the crude and adjusted ORs of *H. pylori* combined with CagA for non-cardia cancer. The crude OR of *H. pylori* infection for non-cardia cancer was 7.0 (95% CI, 3.3–14.8). The highest OR was observed in the *H. pylori* seropositivity and CagA seropositivity [Hp(+)CagA(+)] category (OR, 10.1; 95% CI, 4.4–23.1). The *H. pylori* seropositivity and CagA seronegativity [Hp(+)CagA(−)] category had an estimated OR of 2.4, but this was not statistically significant. After adjustment for confounding variables, the ORs of *H. pylori* and/or CagA with gastric cancer increased.

Table 2 shows the association of environmental factors with the risk of non-cardia cancer. As for smoking, crude ORs for past and current smoking were 3.3 (95% CI, 1.6–6.7) and 2.8 (95% CI, 1.3–5.8), respectively. Past and current smoking remained, in the multivariate analysis, significantly associated with non-cardia cancer. Regarding salt intake, we found a slightly elevated OR (for high-intake category, OR, 1.5; 95% CI, 0.6–3.7), which did not reach statistical significance. As the consumption of miso soup increased, we found a significantly increased OR (for high-intake category, OR, 2.1; 95% CI, 0.9–5.1; P for trend = 0.04). A marginal positive association between rice intake and non-cardia cancer was observed (for the high-intake category, OR, 2.5; 95% CI, 1.0–6.1; P for trend = 0.07).

Table 1. Crude and adjusted odds ratios (ORs) and 95% confidence interval (CIs)[a] of *Helicobacter pylori* infection for non-cardia cancer

	Cases (n = 122)	Controls (n = 235)	Crude OR	95% CI	Adjusted OR[b]	95% CI
H. pylori infection combined with CagA						
H. pylori (−) and CagA (−)	10	84	1.0		1.0	
H. pylori (+) or CagA (+)	112	151	7.0	3.3–14.8	8.2	3.7–18.2
H. pylori (−) and CagA (+)	9	17	5.3	1.7–16.0	6.0	1.8–19.8
H. pylori (+) and CagA (−)	8	27	2.4	0.8–6.9	2.5	0.8–7.4
H. pylori (+) and CagA (+)	95	107	10.1	4.4–23.1	13.4	5.4–33.3

H. pylori infection was defined when one or both serum assays (*H. pylori* and CagA) were positive
JA, Japan Agricultural Cooperatives
[a] Conditional logistic regression analysis
[b] Adjusted for smoking status, JA membership, family history of gastric cancer, total vegetable intake, total fruits intake, and salt intake

Table 2. Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs)[a] of environmental factors for non-cardia cancer

	Cases (n = 122)	Percentage	Controls (n = 235)	Percentage	Crude OR	95% CI	Adjusted OR	95% CI
Smoking[b]								
Never	44	(36.1)	119	(50.6)	1.0		1.0	
Past	39	(32.0)	53	(22.6)	3.3	1.6–6.7	2.8	1.3–6.3
Current	39	(32.0)	63	(26.8)	2.8	1.3–5.8	2.8	1.2–6.5
						0.01		0.03
Salt[c]								
Tertile 1 (8.7)	46	(37.7)	78	(33.2)	1.0		1.0	
Tertile 2 (13.0)	33	(27.0)	78	(33.2)	0.8	0.5–1.3	1.3	0.7–2.7
Tertile 3 (20.4)	43	(35.2)	79	(33.6)	0.9	0.6–1.5	1.5	0.6–3.7
						0.73		0.36
Miso soup[d]								
<3 cups/day	47	(38.5)	100	(42.6)	1.0		1.0	
3 cups/day	54	(44.3)	99	(42.1)	1.2	0.7–1.9	1.8	1.0–3.3
≧4 cups/day	21	(17.2)	36	(15.3)	1.2	0.6–2.4	2.1	0.9–5.1
						0.48		0.04
Pickled vegetables[d]								
Tertile 1 (10.9)	52	(42.6)	79	(33.6)	1.0		1.0	
Tertile 2 (36.6)	33	(27.0)	78	(33.2)	0.7	0.4–1.1	0.6	0.3–1.2
Tertile 3 (79.8)	37	(30.3)	78	(33.2)	0.7	0.4–1.2	0.6	0.3–1.3
						0.22		0.17
Rice[d]								
<4 cups/day	31	(25.4)	62	(26.4)	1.0		1.0	
4 cups/day	64	(52.5)	129	(54.9)	1.1	0.6–1.8	1.2	0.6–2.3
≧5 cups/day	27	(22.1)	44	(18.7)	1.4	0.7–2.8	2.5	1.0–6.1
						0.39		0.07
Total vegetable[e]								
Tertile 1 (119.2)	50	(41.0)	79	(33.6)	1.0		1.0	
Tertile 2 (218.4)	33	(27.0)	78	(33.2)	0.7	0.4–1.2	0.7	0.3–1.4
Tertile 3 (377.0)	39	(32.0)	78	(33.2)	0.8	0.5–1.3	0.9	0.4–2.2
						0.34		0.83
Total fruit[f]								
Tertile 1 (50.7)	44	(36.1)	77	(32.8)	1.0		1.0	
Tertile 2 (142.5)	43	(35.2)	80	(34.0)	1.0	0.6–1.6	1.4	0.7–2.6
Tertile 3 (294.0)	35	(28.7)	78	(33.2)	0.8	0.4–1.3	1.1	0.5–2.4
						0.36		0.73

Tertile 1, lowest tertile; tertile 2, intermediate tertile; tertile 3, highest tertile (median intake)
[a] Conditional logistic regression analysis
[b] Adjusted for *H. pylori* infection, JA membership, family history of gastric cancer, total vegetable intake, total fruit intake, and salt intake
[c] Adjusted for *H. pylori* infection, smoking status, JA membership, family history of gastric cancer, total vegetable intake, total fruit intake, and total energy intake
[d] Adjusted for *H. pylori* infection, smoking status, JA membership, family history of gastric cancer, total vegetable intake, total fruit intake, salt intake, and total energy intake
[e] Adjusted for *H. pylori* infection, smoking status, JA membership, family history of gastric cancer, total fruit intake, salt intake, and total energy intake
[f] Adjusted for *H. pylori* infection, smoking status, JA membership, family history of gastric cancer, total vegetable intake, salt intake, and total energy intake

High intake of pickled vegetables and low intake of total vegetables and fruits was not associated with non-cardia cancer.

The joint effects of environmental factors (smoking and foods) and *H. pylori* infection on the risk for non-cardia cancer are presented in Table 3. As for smoking status and *H. pylori* infection, the adjusted OR for non-cardia cancer was 1.9 (95% CI, 0.4–8.8) for the *H. pylori*-negative smoker group, 6.4 (95% CI, 2.1–19.7) for the *H. pylori*-positive never smoker group, and 19.0 (95% CI, 5.4–67.2) for the *H. pylori*-positive smoker group. An *H. pylori*-positive smoker had 3.0 (95% CI, 1.4–6.6) times the risk of non-cardia cancer compared to an *H. pylori*-positive never-smoker (data not shown in Table 3).

For salt, miso soup, pickled vegetables and rice, the ORs were compared with the *H. pylori*-negative subjects with lower intake as a reference. As for salt intake and *H. pylori* infection, the adjusted OR for gastric cancer was 1.8 (95% CI, 0.4–7.7) for *H. pylori*-negative

Table 3. Joint effect of environmental factors and *H. pylori* infection on the risk for non-cardia cancer

	Cases (n = 122)	Controls (n = 235)	Crude OR	95% CI	Adjusted OR	95% CI	Interaction term
Smoking[a]							
H. pylori (−) and never smoking	4	43	1.0		1.0		
H. pylori (−) and smoking	6	41	2.0	0.5–9.1	1.9	0.4–8.8	
H. pylori (+) and never smoking	40	76	5.3	1.8–15.8	6.4	2.1–19.7	
H. pylori (+) and smoking	72	75	17.7	5.2–60.5	19.0	5.4–67.2	0.52
Salt[b]							
H. pylori (−) and low intake	4	41	1.0		1.0		
H. pylori (−) and high intake	6	43	1.5	0.4–5.9	1.8	0.4–7.7	
H. pylori (+) and low intake	58	76	8.9	2.8–27.6	9.7	3.0–31.7	
H. pylori (+) and high intake	54	74	9.0	2.8–28.3	14.2	3.9–52.3	0.56
Miso soup[c]							
H. pylori (−) and low intake	8	77	1.0		1.0		
H. pylori (−) and high intake	2	7	2.1	0.3–13.7	3.0	0.4–24.1	
H. pylori (+) and low intake	93	122	7.6	3.4–17.0	9.0	3.8–21.3	
H. pylori (+) and high intake	19	29	8.4	3.0–23.4	12.6	4.0–39.4	0.52
Pickled vegetables[c]							
H. pylori (−) and low intake	6	45	1.0		1.0		
H. pylori (−) and high intake	4	39	0.9	0.2–3.5	0.7	0.2–3.3	
H. pylori (+) and low intake	63	73	7.4	2.7–20.2	8.0	2.8–22.8	
H. pylori (+) and high intake	49	78	5.7	2.1–15.7	6.4	2.0–19.9	0.84
Rice[c]							
H. pylori (−) and low intake	8	63	1.0		1.0		
H. pylori (−) and high intake	2	21	0.7	0.1–3.9	0.9	0.2–5.4	
H. pylori (+) and low intake	87	128	5.8	2.5–13.5	7.3	2.9–18.4	
H. pylori (+) and high intake	25	23	11.0	3.9–30.9	18.7	5.6–62.6	0.31
Total vegetable[d]							
H. pylori (−) and high intake	4	36	1.0		1.0		
H. pylori (−) and low intake	6	48	0.9	0.2–3.6	1.0	0.2–4.4	
H. pylori (+) and high intake	48	81	5.5	1.8–16.9	7.6	2.3–25.2	
H. pylori (+) and low intake	64	70	7.5	2.5–22.3	8.5	2.4–29.9	0.60
Total fruit[e]							
H. pylori (−) and high intake	5	39	1.0		1.0		
H. pylori (−) and low intake	5	45	0.8	0.2–3.2	0.9	0.2–3.9	
H. pylori (+) and high intake	44	78	4.8	1.7–13.0	5.8	2.0–16.9	
H. pylori (+) and low intake	68	73	7.9	2.8–21.8	10.6	3.3–33.9	0.32

Salt, pickled vegetable, total vegetable and fruit ; low (below median) intake , high (above median) intake
Miso soup; low intake (<3 cups/day), high intake (≧3 cups/day)
Rice; low intake (<4 cups/day), high intake (≧4 cups/day)
H. pylori infection was defined when one or both serum assays (*H. pylori* and CagA) were positive
[a] Adjusted for JA membership, family history of gastric cancer, total vegetable intake, total fruit intake, and salt intake
[b] Adjusted for JA membership, smoking status, family history of gastric cancer, total vegetable intake, total fruit intake, and total energy intake
[c] Adjusted for JA membership, smoking status, family history of gastric cancer, total vegetable intake, total fruit intake, salt intake and total energy intake
[d] Adjusted for JA membership, smoking status, family history of gastric cancer, total fruit intake, salt intake, and total energy intake
[e] Adjusted for JA membership, smoking status, family history of gastric cancer, total vegetable intake, salt intake, and total energy intake

subjects with a high intake, 9.7 (95% CI, 3.0–31.7) for *H. pylori*-positive subjects with a low intake, and 14.2 (95% CI, 3.9–52.3) for *H. pylori*-positive subjects with a high intake. After adjustment for confounding factors including smoking status, high intake of miso soup tended to increase the ORs of non-cardia cancer in both *H. pylori*-positive and -negative subjects. Regarding rice consumption, the adjusted OR was 7.3 (95% CI, 2.9–18.4) for *H. pylori*-positive subjects with a low intake and 18.7 (95% CI, 5.6–62.6) for *H. pylori*-positive subjects with a high intake. High rice consumption was not associated with non-cardia cancer among *H. pylori*-negative subjects.

ORs were compared with *H. pylori*-negative subjects with a high intake of total vegetables and total fruits as the reference. Low intake of vegetables/fruits did not increase the risk compared with high intake among *H. pylori*-negative subjects. However, a marginal positive association between low intake of total fruits and non-cardia cancer was observed among *H. pylori*-positive subjects.

Additionally, no significant improvement in the regression model was observed when the interaction term between these environmental factors (smoking, food groups, and food items) and *H. pylori* infection was added.

Discussion

In this study, *H. pylori* infection was defined as present when one or both serum assays were positive. Clinical data indicated that the CagA antibody persisted longer after eradication treatment than the antibody detected by *H. pylori* IgG [22]. It seems reasonable to assume that the addition of a test for the CagA antibody will result in a more correct representation of past exposure than the use of the *H. pylori* IgG antibody alone, as Ekstrom et al. [23] suggested.

We confirmed the strong association between *H. pylori* infection and non-cardia cancer. In this study, a significantly increased risk was observed in the *H. pylori* seropositivity and CagA seropositivity [Hp(+)CagA(+)] category, while risk was moderately but not significantly increased between the *H. pylori* seropositivity and CagA seronegativity category. This suggested that CagA-positive *H. pylori* infection had strongly increased the risk for non-cardia cancer compared with *H. pylori*-negative subjects, consistent with previous studies [3–6].

As for smoking status, smoking tended to increase the risk for gastric cancer irrespective of *H. pylori* infection. *H. pylori*-positive smokers showed the highest OR, of 19.0, compared to *H. pylori*-negative never-smokers. Smoking proved to be a risk factor even among subjects with *H. pylori* infection. Some mechanisms of smoking associated with the increased risk of gastric cancer have been suggested. Smokers show lower plasma levels of antioxidants such as vitamin C and beta-carotene [24], and tobacco smoke contains carcinogenic nitrosamines, triggering the carcinogenesis of gastric carcinoma [25]. An increased risk of gastric cancer from smoking was observed in two prospective studies [26,27]. From investigating the joint effects of *H. pylori* and smoking status, Siman et al. [28] suggested that smoking and *H. pylori* were both risk factors for gastric cancer, and that smoking was still a risk factor among *H. pylori*-positive individuals. Brenner et al. [16] found that CagA-positive smokers had an increased risk of non-cardia gastric cancer in a close to multiplicative way, leading to a 16.6-fold risk increase compared with non-smokers without *H. pylori* infection. In a Russian case-control study, smoking had no effect on the risk of gastric cancer in *H. pylori*-negative men, but it was associated with a significantly increased risk in *H. pylori*-positive men (*P* value for interaction, 0.07) [29].

Excessive salt intake is a risk factor supported by experimental and epidemiological studies [10,30,31]. The promoting effects of salt may be caused through a mechanism by which high salt concentrations destroy the mucosal barrier that protects the surface membrane of the stomach [32]. In Mongolian gerbils, the synergistic promoting effects of *H. pylori* infection and a high-salt diet (containing 10% sodium chloride) on gastric carcinogenesis were observed [31]. In the present study, although high salt intake caused a slightly increased OR, it was not statistically significant. In the analysis of joint effects, *H. pylori* infection with a high salt intake had an elevated OR for non-cardia cancer compared with the reference category, but failed to show a statistically significant increase in ORs compared with *H. pylori*-positive subjects with a low intake (data not shown). Part of the reason for this result was the difficulty in estimating the exact amount of salt consumption from the questionnaire. Moreover, we may find a synergistic promoting effect of salt intake on gastric cancer only in subjects who consistently consume high levels of salt.

As miso soup and rice intake increased, we found a steady increase in the risk of non-cardia cancer. Because miso soup is one of the major contributors to sodium intake, this result is plausible. For rice, a marginal positive association was observed. A high rice intake significantly increased the risk (OR, 2.6; 95% CI, 1.1–6.0) compared to low intake even in *H. pylori*-positive subjects. A positive association between high rice intake and *H. pylori* infection has been observed in some epidemiological studies [8,9]. Although a previous study suggested that carbohydrates irritated the gastric mucosa [33], the direct effect of rice on carcinogenesis in the stomach was unclear. As an indirect effect, there is a possibility that rice intake is a marker of salt, salty food, and other dietary factors that are risk factors for gastric cancer.

Vegetables and fruits contain many compounds with anticarcinogenic properties, including carotenoids and vitamin C, and have been considered to be factors that protect against stomach carcinogenesis [10,11]. Our previous study showed the protective effect of mushrooms and cruciferous vegetables on the risk of gastric cancer among the same subjects as those in this present study [12]. The high consumption of total vegetables and fruits did not decrease the risk of non-cardia cancer after adjustment for *H. pylori* infection in our study. In the analysis of *H. pylori* infection and vegetables/fruits, low intake did not show an increased risk for non-cardia cancer compared with *H. pylori*-positive subjects with high intake, although *H. pylori*-positive subjects with low intake of total fruits tended to have an increased risk compared with *H. pylori*-positive subjects with high intake. In a previous study using the same food frequency questionnaire (FFQ), the average intake of vegetables and fruits was 215 g/day and 132 g/day among 18399 men, and 256 g/day and 202 g/day among 20932 women [34]. The lack of association could also be explained by a relatively high intake of these items in the two municipalities of Nagano prefecture comprising the present study area compared with that in other areas

[35]. Kobayashi et al. [36], in a prospective study, suggested that vegetable and fruit intake, even in low amounts, was associated with a decreased risk; however, the risk did not decrease in a stepwise manner as the consumption increased. Therefore the decreased risk may have not been observed in the present study because these study subjects consumed relatively high amounts of vegetables and fruits. Another explanation may be that the protective effect of vegetable consumption, if any, may be modified or masked by other prevalent risk factors, for example, *H. pylori* infection.

The Spearman correlation coefficient for total vegetable intake assessed with FFQ and 14- or 28-day dietary records was relatively low. However, the intake assessed with FFQ was comparable to that with the 14- or 28 days dietary record in the categorization of vegetable intake [18]. Moreover, we had observed an inverse association between vegetable intake and the risk of colorectal cancer in a simultaneously conducted case-control study using the same FFQ [12]. It is, therefore, unlikely that the failure to observe a protective association was due to the relatively low validity of the vegetable intake assessment.

In this study, there was almost no improvement at all in the logistic regression model when the interaction term between these environmental factors and *H. pylori* infection was added. The limited number of cases prohibited a more comprehensive assessment of gastric cancer risk according to the joint classification of subjects by environmental factors and *H. pylori* infection, and led to quite wide confidence intervals for some of the risk estimates. In other words, we might have failed to detect a statistically significant interaction owing to the small number of *H. pylori-negative* cases. Moreover, the high prevalence of *H. pylori* infection and its strong link to gastric cancer may have made precise evaluation of the association between environmental factors and gastric cancer virtually impossible.

There were some limitations in this study. First, the dietary information we collected was about the diet 1 year before the diagnosis. Such dietary information may not actually reflect past dietary habits, which may be more important for carcinogenesis in the stomach. Additionally, one of the major problems of case-control studies is the possibility of recall bias due to knowledge of the disease status. Information on food intake was collected after subsequent diagnosis of gastric cancer, so we could not avoid the recall bias inherent in case-control studies. Furthermore, cases might have changed their dietary habits as a consequence of gastric cancer and atrophic gastritis. Thus, dietary assessment is subject to considerable misclassification. In addition, the diagnosis of *H. pylori* infection (including CagA) was based on immunological tests. The possibility of misclassification of *H. pylori* and CagA seropositivity by immunological tests was not excluded. However, if the misclassification occurred equally among all subjects, the risk of infection linked to the development of gastric cancer was underestimated. Another limitation of case-control studies is their potential selection bias. Among the controls in this study, the percentage of never-smokers was high because of the low number of female smokers. The percentages of past smokers and current smokers were 31.5% and 39.0%, respectively, in the male controls. The percentage of current male smokers in this study was low compared with that in a population-based prospective study of 19576 Japanese men aged 40–59 years (53.4%) [26]. The low prevalence of smokers in the control group may have led to an overestimation of OR regarding cigarette smoking. Because the controls were participants in a medical health check-up program, they were considered to be more health-conscious than the general population. In addition, the JA members were more familiar with health check-up programs than non-members. Thus, we performed careful multivariate adjustment for confounding factors, including JA membership, as mentioned above.

We confirmed the strong association of *H. pylori* combined with CagA with non-cardia cancer. Regarding environmental factors, smoking and high intake of miso soup were associated with non-cardia cancer, regardless of *H. pylori* infection. Although a high rice intake and low fruit intake increased risk only among *H. pylori*-positive subjects, the interaction term was not statistically significant. However, we could not deny the interaction between *H. pylori* infection and environmental factors. Among the various factors studied here, *H. pylori* infection was shown to be the most important factor for non-cardia gastric cancer, indicating that eradication therapy for *H. pylori* would possibly be an effective strategy for reducing the risk of gastric cancer. Our study also indicates that other realistic alternatives may be smoking cessation and dietary modification for non-cardia gastric cancer, irrespective of *H. pylori* status. Further studies in a large number of subjects will be necessary to clarify the interaction between the various risk factors.

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PROSPECTIVE STUDY OF THREE MAJOR DIETARY PATTERNS AND RISK OF GASTRIC CANCER IN JAPAN

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Dietary pattern analysis is an alternative and complementary approach to identify the relationship between diet and the risk of chronic disease. This study was aimed at investigating the associations between dietary patterns and the risk of gastric cancer in Japan. Using baseline data from a prospective study of 20,300 men and 21,812 women, we conducted factor analysis and identified 3 major dietary patterns, healthy, traditional and Western, and calculated the factor scores of each pattern for individuals. During 10 years of follow-up, 400 cases of gastric cancer were identified. We found an inverse association between the healthy pattern and gastric cancer risk in women [rate ratio for highest quartile (RR) = 0.56; 95% CI = 0.32–0.96; *p* for trend = 0.03], but not in men. In contrast, the traditional pattern was significantly associated with the increased risk of gastric cancer in both genders (for men, RR = 2.88, 95% CI = 1.76–4.72; for women, RR = 2.40, 95% CI = 1.32–4.35). The Western pattern was not associated with risk. These associations persisted in histologic subtypes. Our findings support the idea that the healthy pattern decreased the risk of gastric cancer among females, while the traditional pattern increased the risk in both genders.

Key words: *dietary pattern; gastric cancer; histologic subtypes; Japan*

Gastric cancer has been one of the most extensively studied cancers with regard to dietary factors. Previous epidemiologic evidences[1–6] generally indicate that high intakes of vegetable and fruit exert a protective effect and reduce the risk of gastric cancer through a plausible mechanism of modulation of xenobiotic metabolizing enzymes, in particular phase 2 enzymes, while excessive salt and salted food intakes are possible risk factors for gastric cancer. However, many of these associations have thus far been refuted or found to be inconsistent in the light of epidemiologic findings.[7–10]

Although the incidence and mortality rates of gastric carcinoma have declined dramatically in the past 50 years in Japan,[11,12] it still remains one of the leading causes of death, as in many Asian countries.[13] Dietary changes over the last few decades, especially reduced intake of salt and salted foods, increased intake of green-yellow vegetables and dairy foods and Westernized dietary practice have been considered as major plausible reasons for the decreasing trends in gastric cancer in Japan.[11,14]

People eat meals consisting of a variety of foods with complex combinations of nutrients, not isolated nutrients. Because of the complexity of diets, the traditional approach with a single nutrient may potentially be confounded by the interactions between food components that are likely to be interactive or synergistic.[15] This makes it difficult to examine the real associations of dietary factors and disease. These combined effects of various nutrients and foods can be observed when the overall dietary pattern is considered. The overall dietary pattern reflects many simultaneous dietary exposures. Therefore, the examination of the effects of overall food consumption may be an important complementary approach for elucidating relationships between diet and health. Although dietary pattern analyses in relation with cancers have been reported in Western countries,[16–19] few attempts have been made to identify dietary patterns that may be associated with cancer risks in Asian countries, including Japan.

Accordingly, using factor analysis in the present investigation, we identified dietary patterns and evaluated the associations between dietary patterns and gastric cancer risks in a population-based cohort study, the Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) Cohort 1.

MATERIAL AND METHODS

Study cohort

The JPHC Study Cohort 1 is a population-based prospective study launched in 1990. The study cohort included 54,498 residents (27,063 men and 27,435 women) of 14 administrative districts supervised by 4 public health centers (PHCs): Ninohe PHC area of Iwate Prefecture, Yokote PHC area of Akita, Saku PHC areas of Nagano and Ishikawa PHC area of Okinawa. All subjects were born between 1930 and 1949 (40–59 years of age at baseline). The 4 PHC areas were selected to represent the extent of variation in the mortality rate due to gastric cancer based on our previous ecologic studies.[20] The study design has been described in detail previously.[21] The JPHC study was approved by the institutional review board at the National Cancer Center.

Baseline questionnaire

The self-administered food frequency questionnaire (FFQ) includes 44 food groups that were commonly consumed in this study population. Participants indicated their average frequency of consumption for each food group over the past month. For rice, inquiry was made as to the number of bowls consumed per day. The frequency of miso (fermented soybean paste) soup consumption was classified into 4 categories—rarely (< 1 day/week), 1–2 days/week, 3–4 days/week and almost everyday (6 days or more/week)—and the number of bowls per day was asked in the same way as for rice intake. The frequency of other food group items was classified into 4 categories: rarely (< 1 day/week), 1–2 days/

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week, 3–4 days/week and almost everyday (6 days or more/week). For each of 9 nonalcoholic beverage items (green tea, Chinese tea, black tea, other kinds of tea, coffee, milk, soda, fruit juice and vegetable juice), the intake frequency was asked using 6 categories: rarely (< 1 day/week), 1–2 days/week, 3–4 days/week, 1–2 cups/day, 3–4 cups/day and 5 cups or more/day. Questions on the consumption frequency of 5 alcoholic beverages (sake, shouchu, beer, whiskey and other) covered 6 categories (almost never, 1–3 days/month, 1–2 days/week, 3–4 days/week, 5–6 days/week, almost everyday). The selected frequency category for each item was converted to a weekly intake. In calculating the amount of each food item and nutrients, we used serving sizes based on the observed median values from 14- to 28-day diet record data.[22] The diet record data were also used to assess the validity of the questionnaire. The validity and reproducibility of the FFQ used in this study were reported previously.[23]

In addition, participants were asked to respond to a self-administered questionnaire on lifestyle such as sociodemographic characteristics, medical history, use of vitamin supplements, family history of diseases and their history of cigarette smoking and alcohol consumption. A self-administered questionnaire was distributed to 54,498 registered residents (27,063 men and 27,435 women) in 1990 and was collected from 20,665 men (76%) and 22,484 (82%) women. Of 43,149 subjects who responded to the questionnaire, subjects with a self-reported serious illness (cancer, ischemic heart disease, cerebrovascular disease, chronic liver disease) at baseline, and subjects who were not Japanese or had already moved away at baseline, were excluded in this study, after confirmation during the follow-up period. Additionally, subjects who reported extreme total energy intake (upper 2.5% or lower 2.5%) and subjects who reported a past history of cancer (268 men and 598 women) were also excluded. These exclusions left 42,112 subjects (20,300 men and 21,812 women) eligible for the analysis.

Follow-up and identification of cancer cases

We followed all registered cohort subjects from 1 January 1990 up to 31 December 1999. Cases of cancer occurring in the cohort have been identified through continuous surveillance of hospital records, population-based cancer registries and death certificates. The detailed follow-up procedure was described elsewhere.[24] A total of 400 cases of gastric cancer (285 males and 115 females) were documented with histologically confirmed diagnoses made in 1990–1999 as of November 2000. Histologic subdivisions were made as follows: differentiated type (corresponding to intestinal type in Lauren's classification[25]), including papillary adenocarcinoma, tubular adenocarcinoma (well-differentiated type) and tubular adenocarcinoma (moderately differentiated type), and undifferentiated type (corresponding to diffuse type in Lauren's classification), including poorly differentiated adenocarcinoma, mucinous adenocarcinoma and signet ring cell carcinoma. Adenosquamous carcinoma, squamous cell carcinoma, carcinoid tumor, undifferentiated carcinoma and miscellaneous were considered an unclassified type. For analyses of gastric cancer by histologic subgroup, 214 differentiated-type, 159 undifferentiated-type and 27 unclassified-type cancer patients were identified.

Assessment of dietary patterns

Factor analysis (principal components) was conducted to derive dietary patterns based on the 44 food groups and beverages for men and women separately, using the Factor procedure in SAS (version 8; SAS Institute, Chicago, IL). The factors were rotated by an orthogonal transformation (Varimax rotation function in SAS) to achieve a simpler structure with greater interpretability. We considered components with an eigenvalue greater than 1.5, the Scree test and the interpretability of the factors. This served to limit the number of factors, as well as to better identify more meaningful factors. After Varimax rotation, factor scores were saved from the principal component analysis for each individual. All data presented here are from the Varimax rotation. These scores were used for comparison with other lifestyle factors and to estimate associations with gastric cancers. Factor scores were categorized into quartiles based on the distribution of study population for men and women separately. Retained dietary patterns were labeled on the basis of interpretation of the nutritional implications of the data and did not represent *a priori* intake patterns. When the whole cohort was randomly divided into 2 groups, the 3 major patterns were similar between the 2 groups and closely resembled those for the overall sample.

Statistical analysis

All analyses were separately conducted for men and women. To determine the association between dietary factors and gastric cancer, we estimated the adjusted rate ratios (RRs) for each quartile compared with the lowest quartile of each dietary pattern score using Cox proportional hazard models. In these analyses, age, body mass index, total energy intake, education level and family histories of gastric cancer were used as covariates. Smoking habit and alcohol consumption were added in the multivariate models only for men. We tested for linear trends across categories of dietary pattern by assigning each participant the median value for the category and modeling this value as a continuous variable. For gastric cancer, subgroup analyses were performed for differentiated- and undifferentiated-type gastric cancer.

RESULTS

The Scree plot of eigenvalues retained the 3 major patterns for men and women separately, and we thus identified the 3 dietary patterns in the final models. Factor-loading matrices for the 3 major dietary patterns are listed in Table I. The larger the loading of a given food item to the factor, the greater the contribution of that food item to a specific factor, and a negative loading indicates negative association with the factor. Dietary pattern 1 was heavily loaded with vegetables, fruits, soy products, seaweeds, mushroom, milk, beans and yogurt and was called the healthy dietary pattern. Dietary pattern 2 was loaded with pickled vegetables, salted fish and roe, fish, rice and miso soup for both genders with a negative loading for bread and butter. Dietary pattern 2 was additionally loaded with alcoholic beverages (sake, shochu and beer) for men and thus was called the traditional dietary pattern. Dietary pattern 3 was loaded with meat, poultry, cheese, bread and butter and was called the Western dietary pattern. Although the order of their importance varied and in some instances the load of specific food items and alcoholic beverages was not equal for men and women, the major dietary patterns identified separately for men and women proved to be rather similar.

The baseline characteristics of both men and women according to the quartile of dietary pattern scores are shown in Tables II and III, respectively. Among both men and women, participants with a higher healthy pattern score tended to have a higher educational level, to smoke less and to consume more vitamin A, carotenoids, vitamin C, fiber and fat. Participants with a higher traditional dietary pattern score were slightly older, likely to consume more energy and sodium, to have a family history of gastric cancer and to have a lower educational level. Men with a high traditional dietary pattern score were more likely to smoke and drink alcohol. Participants with a higher Western pattern score were younger, likely to smoke and drink and more likely to have higher fat and vitamin A intakes.

The healthy dietary pattern was strongly associated with a lower risk of gastric cancer of females (Table IV). The multivariate-adjusted rate ratios across increasing quartiles of the healthy dietary pattern scores in females were 1.0, 0.57, 0.77 and 0.56 (95% CI = 0.32–0.96; p for trend = 0.03), respectively. No striking differences in associations were seen according to subtype-specific gastric cancer, although more apparent protective effects appeared in the undifferentiated-type gastric cancer: rate ratio for the highest quartile *vs.*. the lowest (hereafter called high/low RR) = 0.46 (95% CI = 0.22–0.96; p for trend = 0.043). In contrast, among males, the healthy dietary pattern was not associated with the risk of

TABLE I – FACTOR-LOADING MATRIX FOR THE 3 MAJOR DIETARY PATTERNS IDENTIFIED BY FACTOR ANALYSIS

	Male			Female		
	Factor 1 (healthy)	Factor 2 (traditional)	Factor 3 (Western)	Factor 1 (healthy)	Factor 2 (traditional)	Factor 3 (Western)
Yellow vegetables	0.63			0.65		
White vegetables	0.64			0.59		
Green vegetables	0.58			0.54		
Fruits	0.57			0.52		
Seaweed	0.56			0.59		
Potatoes	0.56			0.57		
Yogurt	0.46			0.49		
Mushroom	0.47			0.46		
Soy and soy products	0.49			0.47		
Milk	0.34			0.38		
Eggs	0.38			0.36		
Beans	0.29		0.31	0.31		
Japanese tea						
Salted roe		0.64			0.61	0.35
Pickled vegetables	0.30	0.57			0.65	
Dried fishes	0.32	0.57			0.60	
Salted gut		0.57			0.47	0.42
Miso soup		0.43			0.50	
Rice		0.42			0.51	
Fish and shellfish	0.36	0.43		0.31	0.48	
Sake		0.56				
Shochu		0.29				
Beer		0.34	0.23			
Dressing			0.26		−0.32	0.25
Bread		−0.48	0.25		−0.45	0.27
Butter		−0.40	0.40		−0.44	0.37
Mayonnaise	0.37		0.32	0.33		0.36
Cheese			0.48		−0.32	0.38
Beef			0.54			0.45
Pork			0.39			0.48
Poultry			0.40	0.23		0.45
Bacon			0.49			0.55
Liver			0.46			0.38
Soda beverages			0.35			0.42
Fruit juice			0.39			0.40
Vegetable juice			0.38			0.32
Instant noodles			0.34			0.31
Coffee			0.21		−0.31	0.26
Black tea			0.25			0.24
Noodles			0.24			

Absolute values < 0.20 were not listed for simplicity.

gastric cancer. On the other hand, the traditional dietary pattern was positively associated with the risk of gastric cancer in both males and females and also in each gastric cancer subgroup. The multivariate-adjusted RRs across increasing quartiles of the traditional dietary pattern score were 1.0, 1.97, 2.47 and 2.88 (95% CI = 1.76–4.72; p for trend < 0.0001) for males, and 1.0, 1.70, 1.28 and 2.40 (95% CI = 1.32–4.35; p for trend = 0.007) for females, respectively. The positive associations were stronger for male subjects with undifferentiated-type gastric cancer (high/low RR = 4.92; 95% CI = 1.92–12.6). The associations were still clear in men even after alcoholic beverages were excluded in the traditional dietary pattern (results not shown). As for the Western dietary pattern, no significant associations were found for gastric cancer in either males or females. When the same risk models were calculated for gastric cancer of the cardia and distal type, risk associations from separate analysis did not differ from those of total gastric cancer and there were no significant differences in risk associations between subsites.

DISCUSSION

In a population-based prospective study of 42,112 Japanese of the JPHC study, we identified 3 distinct dietary patterns: healthy, traditional and Western. The 3 dietary patterns identified in the present study were similar to those from previous studies among Japanese and Western populations using factor analysis or cluster analysis. It is important to note that the Western pattern in our study was similar to those labeled Western,[26] Western breakfast and meat[27] among the Japanese population and the Western pattern among the U.S.[16,19] and Swedish[17] populations. The healthy pattern in the present study was also similar to healthy,[18] vegetable and fruit[27] and prudent[16,17,19] patterns identified in other studies. These 2 patterns, healthy and Western, were qualitatively similar to those of Western populations. However, interestingly, the traditional pattern was, as expected, a dietary pattern peculiar to Japanese and comparable to the rice/snack pattern identified by Masaki *et al.*[27]

In the Japanese population under study, where gastric cancer is still the leading cause of cancer death among women and the second among men, the risk of gastric cancer was positively associated with the traditional dietary pattern in both males and females and was inversely associated with the healthy dietary pattern among females. The differential associations with the healthy dietary pattern in men and women may be partially explained by the fact that consumption levels of vitamin C and carotenoids and percentage of cigarette smoker were substantially different between genders. The average amounts of dietary vitamin C and carotenoids intake of the highest quartile of healthy pattern were 91 and 2,492 mg/day in men and 139 and 3,948 mg/day in women, respectively. These intake levels among men even in the highest quartile of the healthy pattern may not reach the limit that can affect the risk of gastric cancer. The role of cigarette smoking

TABLE II – BASELINE CHARACTERISTICS ACCORDING TO QUARTILES OF DIETARY PATTERN SCORE IN MALES

	Dietary pattern	Quartile of dietary pattern score			
		1 (lowest)	2	3	4 (highest)
Age (years)	Healthy	48.0 ± 5.8[1]	49.2 ± 5.9	49.9 ± 5.9	50.7 ± 5.9
	Traditional	49.0 ± 5.9	49.1 ± 5.9	49.4 ± 6.0	50.3 ± 5.8
	Western	50.7 ± 5.8	49.5 ± 5.9	49.0 ± 6.0	48.7 ± 5.9
Body mass index (kg/m^2)	Healthy	24 ± 3	24 ± 3	23 ± 3	23 ± 3
	Traditional	24 ± 3	23 ± 3	23 ± 3	23 ± 3
	Western	23 ± 3	24 ± 3	24 ± 3	24 ± 3
Education, college or higher (%)	Healthy	12.6	13.9	14.8	15.8
	Traditional	18.6	17.0	12.9	8.5
	Western	13.1	14.6	14.6	14.8
Current smoker (%)	Healthy	60.8	54.9	51.8	45.1
	Traditional	44.4	50.9	57.2	60.2
	Western	48.9	53.9	53.7	56.3
Drinker, ≥5 times/week (%)	Healthy	51.9	50.6	48.7	43.1
	Traditional	15.5	36.6	61.0	81.0
	Western	40.7	48.5	51.7	53.4
Family history of gastric cancer (%)	Healthy	5.4	6.3	6.8	8.7
	Traditional	3.6	7.3	7.5	8.7
	Western	8.3	7.6	6.4	4.9
Total energy (kcal)	Healthy	1,906 ± 667	2,103 ± 720	2,210 ± 633	2,373 ± 625
	Traditional	1,690 ± 495	2,001 ± 516	2,273 ± 654	2,628 ± 673
	Western	2,112 ± 608	2,083 ± 628	2,108 ± 754	2,289 ± 715
Energy-adjusted nutrient intakes					
Carbohydrates (g)	Healthy	311 ± 52	313 ± 45	311 ± 42	308 ± 38
	Traditional	319 ± 42	316 ± 47	309 ± 44	298 ± 42
	Western	333 ± 39	315 ± 41	303 ± 42	290 ± 45
Dietary fiber (g)	Healthy	6 ± 1	8 ± 1	9 ± 1	10 ± 1
	Traditional	8 ± 2	8 ± 2	8 ± 2	8 ± 2
	Western	9 ± 2	8 ± 2	8 ± 2	8 ± 2
Fat (g)	Healthy	24 ± 7	28 ± 7	32 ± 7	37 ± 8
	Traditional	33 ± 9	30 ± 9	29 ± 8	29 ± 8
	Western	26 ± 8	28 ± 8	31 ± 8	35 ± 9
Sodium (mg)	Healthy	1,876 ± 825	2,134 ± 761	2,279 ± 749	2,367 ± 672
	Traditional	1,778 ± 731	2,078 ± 767	2,288 ± 700	2,513 ± 709
	Western	2,132 ± 724	2,089 ± 758	2,111 ± 755	2,325 ± 840
Vitamin A (mg)	Healthy	2,870 ± 2,981	3,484 ± 3,002	3,944 ± 3,131	4,572 ± 3,366
	Traditional	3,698 ± 3,057	3,538 ± 3,128	3,511 ± 3,044	4,123 ± 3,456
	Western	2,155 ± 1,994	3,122 ± 2,659	3,952 ± 2,817	5,641 ± 3,879
Carotenoid (mg)	Healthy	952 ± 533	1,354 ± 552	1,780 ± 685	2,492 ± 806
	Traditional	1,762 ± 934	1,635 ± 870	1,588 ± 831	1,593 ± 817
	Western	1,559 ± 825	1,542 ± 805	1,626 ± 816	1,851 ± 976
Vitamin C (mg)	Healthy	45 ± 22	61 ± 20	73 ± 21	91 ± 22
	Traditional	63 ± 27	66 ± 27	69 ± 26	73 ± 28
	Western	66 ± 23	63 ± 24	65 ± 24	76 ± 34

[1]Values are mean ± SD.

may be strongly associated with the risk only in men.[24] The differential association between men and women may also be explained partially by the contribution of pickled vegetables (factor-loading matrix of 0.30) and dried fishes (0.32) to the healthy dietary pattern in men. Similar risk associations were found between histologic subtypes and anatomic subsites.

Many case-control studies of gastric cancer[6,8] that focused on a single or a few nutrients or foods have previously found inverse associations with vegetable and fruit consumption. However, the evidences from prospective cohort studies[7,9,28] and from a nutrition intervention trial with multiple vitamin/mineral supplementation[29] have been inconsistent.

Four previous epidemiologic studies examined the associations between dietary pattern and gastric cancer risk. In the cross-sectional study of Chinese,[30] there were no clear associations between each dietary pattern and gastric cancer risk. In a case-control study of U.S.$_{18}$ and Italian populations,[31] the risk of gastric cancer was positively associated with the high-meat dietary pattern or the traditional pattern (high intake of protein, starch, alcohol and nitrite) and negatively associated with the vitamin-rich pattern. In a prospective study of male Japanese,[27] the risk ratio associated with the highest tertile compared to the lowest tertile was 0.78 (95% CI = 0.42–1.44) for vegetable and fruit pattern after adjustment for potential confounders. These studies were limited by the small number of subjects, recall bias of dietary assessment due to the study design and lack of control for potential confounders.

With regard to the associations between salt and the risk of gastric cancer, although epidemiologic and experimental data have generally suggested that excessive salt intake and the consumption of salted foods probably increase the risk of gastric cancer,[5,32,33] these associations have not been fully consistent and there is no solid evidence for a causal role.[34] Such discrepancies among previous studies indicate the difficulties in the estimation and measurement of dietary salt intake. In addition, these studies are not fully interpretable because of lack of information concerning the presence of genotoxic carcinogens present in the salted foods consumed.[34] Many kinds of salted foods contain possible carcinogens because salt contaminated with nitrates and nitrites has been used in the salting process. Excessive salt may also increase the mutagenicity of nitrosated foods.[32] It has also been suggested that the salt concentration, rather than the total dose, is the more important determining factor.[34] Compared with Western countries, highly salted foods are commonly consumed in some Southeast Asian countries, including Japan.[35] The traditional dietary pattern in the present study includes many kinds of salted foods, such as pickled vegetables, salted fish and roe and dietary habits related to this pattern, which may be an indirect marker of genotoxic carcinogen exposure. Unlike the individual food or nutrient approach, this dietary pattern

TABLE III - BASELINE CHARACTERISTICS ACCORDING TO QUARTILES OF DIETARY PATTERN SCORE IN FEMALES

	Dietary pattern	Quartile of dietary pattern score			
		1 (lowest)	2	3	4 (highest)
Age (years)	Healthy	48.9 ± 5.9[1]	49.4 ± 5.8	49.7 ± 5.8	50.4 ± 5.9
	Traditional	48.6 ± 5.9	49.1 ± 5.9	49.8 ± 5.9	50.9 ± 5.5
	Western	50.9 ± 5.7	49.7 ± 5.8	49.1 ± 5.9	48.8 ± 5.8
Body mass index (kg/m^2)	Healthy	24 ± 3	24 ± 3	23 ± 3	23 ± 3
	Traditional	24 ± 4	23 ± 3	23 ± 3	24 ± 3
	Western	24 ± 3	24 ± 3	24 ± 3	24 ± 3
Education (college or higher) (%)	Healthy	9.8	10.7	12.1	15.6
	Traditional	16.5	14.0	10.4	7.3
	Western	11.9	11.8	12.3	12.3
Current smoker (%)	Healthy	9.1	5.0	4.9	3.8
	Traditional	7.4	6.4	4.9	4.0
	Western	3.9	5.4	6.1	7.4
Drinker (≥ 5 times/week) (%)	Healthy	5.2	3.4	3.4	3.3
	Traditional	2.6	4.4	4.1	4.2
	Western	2.9	3.3	4.1	5.1
Family history of gastric cancer (%)	Healthy	5.3	6.5	7.2	8.6
	Traditional	3.1	7.9	8.9	7.6
	Western	7.8	7.1	6.6	6.0
Total energy (kcal)	Healthy	1,229 ± 415	1,352 ± 332	1,434 ± 342	1,569 ± 330
	Traditional	1,228 ± 336	1,354 ± 379	1,433 ± 328	1,569 ± 380
	Western	1,273 ± 317	1,323 ± 333	1,393 ± 365	1,594 ± 407
Energy-adjusted nutrient intakes					
Carbohydrates (g)	Healthy	220 ± 25	212 ± 21	206 ± 20	198 ± 18
	Traditional	204 ± 24	208 ± 23	211 ± 21	213 ± 21
	Western	217 ± 22	211 ± 21	207 ± 21	201 ± 23
Dietary fiber (g)	Healthy	7 ± 1	9 ± 1	10 ± 1	12 ± 1
	Traditional	9 ± 2	10 ± 2	10 ± 2	10 ± 2
	Western	10 ± 2	10 ± 2	9 ± 2	10 ± 2
Fat (g)	Healthy	26 ± 7	31 ± 7	34 ± 7	39 ± 8
	Traditional	34 ± 9	33 ± 9	32 ± 8	31 ± 8
	Western	28 ± 8	31 ± 8	33 ± 7	38 ± 8
Sodium (mg)	Healthy	2,061 ± 851	2,185 ± 730	2,253 ± 680	2,261 ± 586
	Traditional	1,683 ± 642	2,057 ± 650	2,369 ± 613	2,653 ± 599
	Western	2,112 ± 713	2,125 ± 716	2,149 ± 697	2,375 ± 732
Vitamin A (mg)	Healthy	3,627 ± 3,758	4,454 ± 3,816	4,945 ± 3,976	5,788 ± 4,090
	Traditional	5,398 ± 4,130	4,604 ± 3,933	4,415 ± 3,815	4,396 ± 3,990
	Western	3,223 ± 2,721	4,045 ± 3,329	4,989 ± 3,893	6,557 ± 4,887
Carotenoid (mg)	Healthy	1,683 ± 807	2,389 ± 861	3,027 ± 987	3,948 ± 977
	Traditional	2,828 ± 1,296	2,801 ± 1,284	2,740 ± 1,188	2,678 ± 1,163
	Western	2,825 ± 1,247	2,651 ± 1,172	2,662 ± 1,169	2,908 ± 1,327
Vitamin C (mg)	Healthy	79 ± 38	102 ± 32	119 ± 30	139 ± 29
	Traditional	95 ± 39	109 ± 39	115 ± 36	120 ± 39
	Western	107 ± 34	104 ± 35	106 ± 35	122 ± 49

[1]Values are mean ± SD.

approach to overall consumption of salt and salted foods is associated with a significantly increased risk of gastric cancer.

The traditional dietary pattern, which is highly loaded with salted foods, miso soup and rice, is a typical dietary pattern of Japan, where both salt/salted food intake and gastric cancer incidence varied significantly and were well correlated at the population level.[36] The associations with salt and salted food intake were always attenuated after stratifying by study area.[37] Considering these large variations of salty food consumption between each study area with limited variation within each area, adjustment of PHC area may have underestimated the true association. Therefore, we did not include PHC areas as confounders in multivariate model.

It is important to note that dietary patterns are associated with health behaviors, lifestyle and sociodemographic factors.[38,39] As shown in Tables II and III, major dietary patterns were associated with demographic factors and lifestyle habits. Therefore, we cannot exclude the possibility that not only dietary factors defined as dietary patterns, but also their related demographic and lifestyle factors may affect the gastric cancer risk.

This cohort study has been conducted in a large sample of men and women from the general Japanese population. One of its strengths is the higher rate of participation and completeness of follow-up, indicating that selection bias due to loss of follow-up is highly unlikely. Another strength is the prospective design; the diet was measured before the disease was diagnosed, which diminishes the probability of recall bias of dietary intake. We also controlled extensively for potential confounders. However, it is likely that unmeasured or unidentified risk factors may have affected the study results. For example, we could not adjust for *Helicobacter pylori* infection, a strong risk factor for gastric cancer. Previous ecologic study by our group has shown a prevalence of *H. pylori* seropositivity from 63% to 76% among subjects 40–49 years of age in these 4 study areas.[35] Although a possible interaction between a high-salt diet and *H. pylori* infection in gastric cancer has been suggested,[40,41] a recent experimental study showed that *H. pylori*-associated gastric cancer in INS-GAS mice is gender-specific and there was no synergism in this mice model between a high-salt diet and *H. pylori* infection.[42] Nevertheless, this infection may affect the present results as a potential confounder of the association between dietary factors and the risk of gastric cancer.

The present study has several limitations. Although our questionnaire requested detailed information regarding consumption of food and food groups, it was a short version that included only 44 food items. The number of total cohort subjects was not small, but there were few cancer cases, particularly in the subgroup analysis. Accordingly, the risk estimates may be moderately imprecise and more attention is needed to interpret the findings of the subgroup analysis, especially for women.

TABLE IV – MULTIVARIATE RATE RATIOS OF GASTRIC CANCER WITH 95% CONFIDENCE INTERVALS ACCORDING TO QUARTILE OF THE 3 MAJOR DIETARY PATTERNS, JPHC STUDY, 1990–1999

	Quartiles (male)				*p* for trend	Quartiles (female)				*p* for trend
	1 (low)	2	3	4 (high)		1 (low)	2	3	4 (high)	
Healthy dietary pattern										
Total gastric cancer										
Person years	47,265	47,481	47,622	47,710		52,124	52,338	52,530	52,289	
Cases	57	66	74	88		36	23	32	24	
RR (95% CI)	1.00	1.00 (0.70–1.45)	1.06 (0.74–1.53)	1.13 (0.78–1.63)	0.39	1.00	0.57 (0.33–0.97)	0.77 (0.47–1.26)	0.56 (0.32–0.96)	0.03
Differentiated type										
Cases	36	38	43	57		12	7	12	9	
RR (95% CI)	1.00	0.91 (0.57–1.45)	0.97 (0.61–1.53)	1.11 (0.70–1.76)	0.29	1.00	0.53 (0.21–1.34)	0.81 (0.35–1.88)	0.62 (0.25–1.54)	0.31
Undifferentiated type										
Cases	17	27	22	27		21	14	19	12	
RR (95% CI)	1.00	1.37 (0.73–2.58)	1.10 (0.57–2.15)	1.24 (0.64–2.40)	0.71	1.00	0.57 (0.29–1.15)	0.79 (0.42–1.49)	0.46 (0.22–0.96)	0.04
Traditional dietary pattern										
Total gastric cancer										
Person years	46,883	47,043	47,711	48,441		51,611	52,011	52,487	53,172	
Cases	30	62	81	112		17	30	23	45	
RR (95% CI)	1.00	1.97 (1.25–3.12)	2.47 (1.55–3.94)	2.88 (1.76–4.72)	< 0.0001	1.00	1.70 (0.93–3.12)	1.28 (0.68–2.44)	2.40 (1.32–4.35)	0.007
Differentiated type										
Cases	20	41	50	63		5	9	10	16	
RR (95% CI)	1.00	2.05 (1.16–3.62)	2.37 (1.32–4.28)	2.67 (1.42–5.02)	< 0.0001	1.00	1.82 (0.60–5.49)	1.79 (0.60–5.39)	2.40 (0.83–6.97)	0.06
Undifferentiated type										
Cases	7	19	23	44		11	16	12	27	
RR (95% CI)	1.00	2.50 (1.02–6.12)	3.27 (1.32–8.12)	4.92 (1.92–12.6)	0.006	1.00	1.32 (0.60–2.89)	1.03 (0.45–2.37)	2.31 (1.09–4.89)	0.03
Western dietary pattern										
Total gastric cancer										
Person years	47,649	47,862	47,309	47,258		52,618	52,302	52,274	52,086	
Cases	83	77	64	61		32	27	27	29	
RR (95% CI)	1.00	0.99 (0.71–1.37)	0.88 (0.63–1.24)	0.85 (0.60–1.38)	0.45	1.00	0.94 (0.56–1.57)	0.92 (0.54–1.56)	1.13 (0.66–1.93)	0.42
Differentiated type										
Cases	48	46	44	36		12	7	13	8	
RR (95% CI)	1.00	1.07 (0.71–1.62)	1.07 (0.70–1.64)	0.88 (0.56–1.38)	0.45	1.00	0.67 (0.26–1.70)	1.23 (0.54–2.77)	0.86 (0.34–2.22)	0.68
Undifferentiated type										
Cases	30	24	18	21		17	15	14	20	
RR (95% CI)	1.00	0.78 (0.44–1.37)	0.64 (0.35–1.17)	0.78 (0.44–1.40)	0.96	1.00	0.96 (0.48–1.93)	0.87 (0.42–1.81)	1.40 (0.70–2.78)	0.30

Multivariate adjustment included age (as a continuous variable), body mass index (as a continuous variable), energy intake (as a continuous variable), education level, family history of gastric cancer (yes, no), smoking status (for males) and alcohol drinking (for males).

The possibility of histologic misclassification cannot be ruled out. Histologic typing is inherently subjective, lacks gold-standard measures and depends on the judgment of pathologists.[43] Furthermore, a review of pathologic slides by even one pathologist in a subsample was not practical in this large multicenter study. This limitation may have led to histologic misclassification to some extent and resulted in the absence of any difference in the findings according to the histologic subtypes.

Factor analysis is inherently arbitrary and subjective on the selection of included variables, the number of retained factors, the method of rotation and the labeling of identified factors.[15,44] We repeated the same analyses with varying numbers of factors and when randomly dividing the sample into 2 groups (both in total subjects and for each gender) to examine whether these subjective choices affected the reproducibility of our findings. The results showed very similar dietary patterns. Also, we adhered as closely as possible to the established empirical guidelines for the principal component method of factor analysis. Moreover, the dietary patterns defined in this analysis were not established *a priori* but based on the actual data. The nutritional implications of the 3 dietary patterns were generally understandable.

The dietary pattern approach using factor analysis is population-dependent and may differ according to the geographic area, race, culture, *etc.* Hence, the generalizability of the results of this method is a critical concern. The fact is, different investigations within the same[26,27] or even various populations[16,17,19] generated similar dietary patterns.

In conclusion, the major dietary patterns of the Japanese were identified using factor analysis, and the present findings indicated that the healthy pattern decreased the risk of gastric cancer, while the traditional pattern increased the risk of gastric cancer.

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APPENDIX

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Impact of tobacco smoking on subsequent cancer risk among middle-aged Japanese men and women: data from a large-scale population-based cohort study in Japan—the JPHC study

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Abstract

Background. The present study aimed to obtain a relevant epidemiological index of the impact of tobacco smoking on the subsequent risk of cancer in Japan.

Methods. We conducted a cohort analysis on the possible association between tobacco smoking habits and total cancer risk among a middle-aged Japanese population, using a large-scale population-based cohort of 92,792 subjects (44,521 men and 48,271 women) with 10-year follow-up.

Results. During 1990–2001, 4,922 cases of cancer (2,969 men and 1,953 women) were newly diagnosed. From the baseline questionnaire, 52.2% of men were current smokers and they presented a significantly increased hazard ratio (HR) of subsequent cancer occurrence compared with never-smokers [HR 1.64, 95% confidence interval (95% CI) 1.48–1.82]. Only 5.6% of women were current smokers and their HR also represented a significant increase (HR 1.46, 95% CI 1.21–1.75). The corresponding population attributable fraction (PAF) (%) of total cancer incidence in men was 22.4% (95% CI 15.7%–28.5%) and 7.0% (95% CI 3.7%–10.3%) in relation to current and past exposures to tobacco smoke. In women, the PAF was only 2.2% and 0.6% due to the low prevalence of current and former smokers.

Conclusions. Our results suggest that 29% of male cancer and 3% of female cancer would be preventable in Japanese middle-aged population by avoidance of tobacco smoking.

Keywords: Smoking; Cohort study; Cancer incidence; Population attributable fraction

Introduction

Tobacco smoking has been established as the most important preventable risk factor for cancer at various sites [1]. A considerable number of experimental and epidemiological studies have cumulatively underscored a causal association [2] and tobacco control is currently the key target of most cancer prevention strategies in any part of the world [3], despite the low success rate [4].

In Japan also, tobacco smoking poses the most important public health problem. Even the recent prevalence of current smokers has remained nearly 50% in males, and smoking is increasing in the young female population [5]. Since most Japanese now acknowledge the harm done, the current need is to implement practical tobacco control measures with specific numerical targets appropriate for the Japanese population. Reliable and sufficient evidences derived from the Japanese population are therefore needed. Estimation of the expected effectiveness of primary prevention such as tobacco control requires the calculation of the fraction of the population incidence rate of a cancer that can be attributed

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to tobacco smoking [3]. However, existing evidences on tobacco smoking and subsequent cancer risk in Japan have been limited. Most have focused on cancer death [6–11], and there has been no epidemiological evidence targeted to total cancer incidence.

We launched a large-scale population-based prospective study in 1990 using 11 public health center-based areas throughout Japan with 140,420 middle-aged residents, using questionnaire surveys, blood samples, health screening data and a thorough follow-up system [12]. The average follow-up time is nearly 10 years now and a sufficient number of newly occurring cancers has been accumulated.

Therefore, to obtain a relevant epidemiological index of the impact of tobacco smoking on total cancer incidence, we conducted a cohort analysis on the association between tobacco smoking habits and the risk of occurrence of all sites of cancer among the Japanese population.

Materials and methods

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) was launched in 1990 for Cohort I and in 1993 for Cohort II. Cohort I comprised five prefectural public health center (PHC) areas: Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture) and Katsushika (metropolitan Tokyo). Cohort II comprised six PHC areas: Mito (Ibaraki Prefecture), Kashiwazaki (Nigata Prefecture), Chuo-higashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture) and Suita (Osaka Prefecture). Details of the study design were described elsewhere [13]. This study was approved by the institutional review board of the National Cancer Center. In the present analysis, Katsushika and Suita PHC areas were not included since different definitions of study population were applied.

The study population was defined to be all registered Japanese inhabitants in the remaining nine PHC areas (27 municipalities), aged 40–59 years old in Cohort I and 40–69 in Cohort II at the beginning of each baseline survey. They were identified by population registries maintained by local municipalities. Initially, 116,896 subjects were identified as eligible for the study population. During the follow-up, however, 210 subjects were found to be ineligible for the study and excluded because of non-Japanese nationality (n = 51), late reports of out-migration before the start of the follow-up (n = 156) and age ineligibility due to wrong 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 self-administered questionnaire survey, which included smoking history and other lifestyle factors, was conducted in 1990 for Cohort I and in 1993–1994 for Cohort II. A total of 95,376 subjects responded to the questionnaire, with a response rate of 82%. Among them, 2,062 subjects with a previous or current history of cancer at any site were excluded from further analysis.

The questions on smoking habits included current and former smoking status, age at initiation of smoking and average number of cigarettes smoked per day. For the analysis on smoking habit, status was categorized as never-, former-, and current smoker, the last being further divided by the number of cigarettes per day (≤19, 20–29 and ≥30), age started (≥25 years old, 21–24, ≤20) and pack-years of smoking (≤19, 20–29, 30–39, ≥40). After excluding 522 subjects for whom no smoking status information was available, 92,792 subjects (44,521 men and 48,271 women) remained for the present analysis.

Subjects were followed from 1st January of each year of the baseline survey up to 31st December, 2001. Residence status including survival was confirmed annually through the residential register kept in each municipality of the study areas. For those who moved out of the area, we contacted the municipal office to which they had moved. Inspection of the resident register is available to anyone under the Family Registration Law. Information on the cause of each death was supplemented by checking against death certificate files with permission. The resident and death registration in Japan is required by the Family Registration Law and is believed to be complete. Among the study subjects, 4,991 (5.4%) died, 5,319 (5.7%) moved out, and 46 (0.05%) were lost to follow-up within the follow-up period.

Occurrence of cancer was identified by active patients' notification from local major hospitals in the study area and data linkage with population-based cancer registries with permission. Death certificate information was used as a supplementary information source. The topography and morphology of each case were coded using the International Classification of Diseases for Oncology, 2nd ed. [13]. In our cancer registry system, the proportion of cases for which information was available only from death certificates was 2.3% during the study period. This was considered satisfactory quality for the present study. For the present analysis, the earliest information on diagnosis was used for multiple primary cancers at different times, and the information on the most advanced cases for those occurring at the same time. Accordingly, 4,922 newly diagnosed cancer cases (2,969 men and 1,953 women) and 2,132 cases of cancer deaths (1,411 men and 721 women) identified up to 31st December, 2001, were used for the analysis of smoking habits.

Person-years of follow-up were counted from 1st January of the baseline survey. Person-years of follow-up were counted until the date of occurrence of any cancer, the date of migration out of the study areas, the date of death or the end of the study period, 31st December, 2001, whichever came first. For the 46 persons lost to follow-up, the last confirmed date of their presence in the study area was used as the date of censoring.

The outcome of this study was defined as newly occurring cancers and mortality from cancer during the study period. Hazard ratios (HRs) and their 95% confidence

intervals (95% CI) were used to describe the relative risk of all sites of cancer occurrence associated with smoking habits at baseline. The Cox proportional hazards model was employed for calculations, controlling for potential confounding factors, namely, age at baseline (continuous), study area (nine PHC areas), weekly ethanol intake (none, occasionally, <150 g, 150–299 g, 300–449 g, ≥450 g for men, and none, occasionally, <100 g, ≥100 g for women), body mass index (≤18.9, 19.0–20.9, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, ≥30.0) and green vegetable intake (everyday, less). These variables were either known or suspected risk factors for cancer or had been found to be associated with risk of cancer on the basis of previous results [10,14,15]. To evaluate the linear trend, scored variables were included in the model.

To express the impact of tobacco smoking for overall cancer occurrence and death in this population, the population attributable fraction (PAF) (%) was estimated. This is the fraction of the population incidence or death rate of cancer that can be attributed to a particular cause [3], in other words, the reduction of the incidence that would be achieved if the population had been entirely unexposed [16]. PAF was estimated as pd × (HR − 1/HR), where pd is the proportion exposed to the risk factors. This formula is noted to be more valid than the popular formula: Pe × (RR − 1) / (Pe × (RR − 1) + 1), where Pe is the proportion of source population exposed to the risk factor when a confounding variable exists [17]. Ninety-five percent confidence intervals of adjusted PAF were estimated by the formula of Greenland [18].

Stata version 8 [19] was used to perform the statistical analyses.

Results

During 888,070 person-years of follow-up (average follow-up period: 9.6 years) of 92,792 subjects (44,521 men and 48,271 women), a total of 4,922 cases of newly diagnosed cancer (2,969 men and 1,953 women) and 2,132 cancer fatalities (1,411 men and 721 women) were available for the analyses. In men, stomach cancer occurred most commonly (n = 781, 26.3%), followed by cancer of the lung (n = 400), colon (n = 376) and liver (n = 239). In women, cancers most commonly diagnosed were of the breast (n = 345, 17.7%), followed by stomach (n = 283), colon (n = 221) and lung (n = 139). At baseline (Table 1), 24.3% of men were never-smokers, 52.3% were current smokers and 23.4% had stopped smoking, 92.7% of women had never smoked, only 5.9% were current smokers and 1.4% had stopped smoking before baseline. Both in men and women, current smokers tended to have higher consumption of ethanol and lower body mass index than never- and former-smokers.

Tables 2 and 3 showed HRs and their 95% CIs for all sites of cancer incidence and death with reference to baseline smoking status. In men (Table 2), current smoking increased the HR of total cancer incidence (HR 1.64; 95% CI 1.48–1.82). Former-smokers also showed slightly but significantly increased HR (HR 1.37; 95% CI 1.22–1.54). Similar risks were observed for total cancer death (current: HR 1.78; 95% CI 1.53–2.09; former: HR 1.35; 95% CI 1.13–1.98). Further analysis showed an increasing risk trend by increased daily cigarette consumption, increased pack-years of consumption and decreased age of initiation to smoking for total cancer incidence. For total cancer death, an increased tendency was observed only for lower age of initiation to smoking. In women (Table 3), the significantly increased risks were also observed for total cancer incidence, where current smokers had a HR of 1.46 (95% CI 1.21–2.75) and similar values for former-smokers (HR = 1.47; 95% CI 1.05–2.05). For total cancer death, however, former-smokers did not show an

Table 1
Baseline characteristics of the study subjects by smoking status

		Smoking status			
		Total	Never	Former	Current
Men					
Number of subjects		44,521	10,838	10,422	23,261
Proportion (%)			24.3	23.4	52.3
Age (years) ± SD		52.9 ± 7.9	53.0 ± 7.5	54.7 ± 8.3	52.1 ± 7.8
Alcohol drinking status (%)	none	23.1	26.9	24.1	20.9
	occasional	9.4	12.7	8.2	8.5
	<150 g/week	22.2	26.6	23.3	19.5
	150–299 g/week	19.9	16.8	20.5	21.2
	300–449 g/week	13.2	9.0	12.9	15.3
	≥450 g/week	12.2	8.0	11.0	14.6
Body mass index (%)	≤18.9	4.1	2.9	3.2	5.0
	19.0–20.9	14.5	11.0	11.7	17.4
	21.0–22.9	25.7	22.9	24.1	27.8
	23.0–24.9	27.9	29.7	30.0	26.1
	25.0–26.9	16.6	19.5	18.6	14.4
	27.0–29.9	9.0	11.2	10.0	7.5
	≥30.0	2.2	2.8	2.4	1.8
Green vegetable intake (%)	less	75.8	72.2	73.7	78.4
	everyday	24.2	27.8	26.3	21.6
Women					
Number of subjects		48,271	44,773	658	2,840
Proportion (%)			92.7	1.4	5.9
Age (years) ± SD		53.3 ± 8.0	53.5 ± 8.0	52.6 ± 8.4	51.6 ± 7.8
Alcohol drinking status (%)	none	79.4	81.2	58.5	55.5
	monthly	9.8	9.5	15.6	13.0
	<100 g/week	7.3	6.9	15.0	12.3
	≥100 g/week	3.5	2.4	10.9	19.2
Body mass index (%)	≤18.9	5.3	5.0	5.4	9.2
	19.0–20.9	15.2	15.0	13.8	18.5
	21.0–22.9	26.0	26.1	22.8	24.9
	23.0–24.9	24.6	25.0	23.7	19.3
	25.0–26.9	15.5	15.6	17.8	13.9
	27.0–29.9	10.1	10.1	11.5	9.8
	≥30.0	3.3	3.2	5.0	4.4
Green vegetable intake (%)	less	68.7	68.3	70.6	75.0
	everyday	31.3	31.7	29.4	25.0