Methods

Study cohort

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC study) has been partially reported on elsewhere [20]. Briefly, two population-based cohorts of 57,591 men and 59,103 women were established from public health center (PHC) areas in January 1990 (cohort I) and January 1993 (cohort II). Cohort I comprised 14 administrative districts supervised by four PHCs; Cohort II comprised 13 administrative districts supervised by five PHCs. The study population was defined to be all inhabitants in the study areas aged 40- to 59-years-old in Cohort I and 40- to 69-years-old in Cohort II at the beginning of each study. Inhabitants were identified using residence registries maintained by local governments.

Baseline survey

A self-administered questionnaire that included smoking and dietary habits, in addition to other lifestyle factors and medical history, was distributed to all eligible registered residents in 1990 for Cohort I and in 1993 for Cohort II. Completed questionnaires were collected from 45,452 men (20,658 in Cohort I; 24,794 in Cohort II) and 49,924 women (22,482 in Cohort I; 27,442 in Cohort II). Response rates were 79% for men and 84% for women. A further 680 men and 1358 women with a history of cancer at any site were excluded from analysis.

A food frequency questionnaire asking about the average consumption of 44 food items during the previous month was used in Cohort I. The questionnaire included three items on fresh vegetables ('green leafy vegetables such as spinach'; 'yellow vegetables such as carrot or pumpkin'; and 'white vegetables such as Chinese cabbage, radish, tomato or cucumber'), one item on total fruit and two items on juices (vegetables and fruit). With regard to Cohort II, a food frequency questionnaire covering 52 food items included three items on vegetables ('green vegetables', individual items for 'carrots' and 'tomatoes'), two items on individual fruits ('apple', 'citrus') and two items on juices (vegetables and fruit). Frequency of consumption for vegetables and fruit was asked using four categories in Cohort I: '<1 day/week', '1–2 days/week', '3–4 days/week', and 'almost daily'. Cohort II added an additional category of 'never use'. For the two juices, further information on cups/day was requested for those drinking daily.

For calculating amount of vegetable and fruit intakes, portion size and content of each food item were prespecified based on observed median values on 14–28 day diet record data [21]. This diet record was conducted to assess validity of the questionnaire for Cohort I. Spearman correlation coefficients between diet record and questionnaire in men (n = 94) and women (n = 107), were 0.26 and 0.36 for total vegetable intake (g/day; defined as the sum intake of green, yellow and white vegetables), and 0.52 and 0.40 for total fruit intake (g/day), respectively.

In this study, tofu, beans, and potatoes, were not included in measurements of total vegetable intake because of their high protein and starch content, respectively, compared with other vegetables.

Smoking and other covariates

For both Cohorts I and II, questions on smoking habits 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. We classified subjects by smoking status (never, past, or current), quantity among current smokers (1–19, 20–29, or 30+ cigarettes/day), and duration of smoking (1–19, 20–29, or 30+ years).

Current weight (kg) and height (m) were requested and body mass index (weight/height^2) calculated. Information on consumption of pickled vegetables, highly salted fish roe or gut and salted or dried fish were collected and converted to gram equivalents, and categorized as low, middle, or high third intakes. Subjects also provided information on use of multivitamins or vitamins A, C, and E ('<1 day/week', or '1+ days/week'), frequency of alcohol intake ('<1 day/week', '1–2 days/week', '3–4 days/week', '5–6 days/week', or 'daily'), and frequency of sport in leisure time ('<1 time/week', or '1+ times/week").

Follow-up

We followed subjects from January 1, 1990 in Cohort I and January 1, 1993 in Cohort II through to December 31, 1999. Incident cases of lung cancer occurring in the two cohorts were identified through continuous surveillance of hospital records, population-based cancer registries and death certificates. In two of the five PHCs, prefecture-wide cancer registries were available. Site of origin and histological type were coded using the International Classification of Diseases for Oncology, second edition (ICD-O-2). A total of 428 newly diagnosed lung cancer cases (329 men, 99 women) were identified among 44,772 men and 48,566 women. Diagnosis of lung cancer was based on histological examination of specimens from surgery or autopsy, biopsy or

cytology in 374 cases (87.4%), while diagnosis of the remaining 12.6% of cases was based on clinical findings or unspecified evidence. Histological type was classified into adenocarcinoma, squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and other histological types according to World Health Organization histological classifications for lung tumors [22].

Statistical analysis

We calculated person-years of follow-up for each subject from the start of the study until date of diagnosis of lung cancer, date of migration out of the study area, date of death or end of follow-up, whichever occurred first. The Cox proportional hazards model was used to estimate age-, gender-, and area of residence-adjusted and multivariate-adjusted relative risks (RRs) of vegetable and/or fruit intake for lung cancer. To obtain a summary measure of results from Cohorts I and II, the two RRs estimates were pooled using inverse-variance weighting [23]. Tests of heterogeneity were used to evaluate whether associations differed between Cohort I and Cohort II. Results are shown separately whenever statistically significant heterogeneity was seen.

We divided vegetable only, fruit only, and vegetables and fruit consumption into low, middle, and high thirds with almost equal numbers of subjects in each, to estimate dose–response relationships, with the lower-third group as the reference category. To test linear trends, consecutive integers were given for each category. Covariates included in the models to obtain adjusted relative risks were age, gender, area, sports in leisure time, body mass index, consumption of pickled vegetables, highly salted fish roe or gut and salted or dried fish, weekly use of vitamin supplements, frequency of alcohol intake, smoking status, cigarette number per day, and years of smoking. Age and body mass index were treated as continuous variables, and indicator variables were used for other factors.

Results

During 401,382 and 330,588 person-years of follow-up, 177and 251 newly diagnosed cases of lung cancer were reported from participants in Cohorts I and II, respec-

Table 1. Background information for Cohorts I and II according to categories of vegetables consumption

	Cohort I			Cohort II		
	Low	Middle	High	Low	Middle	High
Men						
No. of subjects	7993	6280	6093	9757	6847	7803
No. of lung cancer cases	47	46	41	84	49	62
Mean age (years)	48.9	49.5	50.2	53.0	54.3	54.3
Mean BMI (kg/m^2)	24.1	24.1	24.0	24.0	24.0	24.1
Alcohol intake (%)						
Never drinker	21.1	20.5	20.3	21.0	20.4	18.8
Daily drinker	37.0	37.2	42.3	43.3	43.7	41.5
Cigarette smoking						
Ever smoker (%)	77.7	74.8	74.9	78.4	74.1	72.2
Current smoker (%)	56.1	51.6	51.1	56.4	49.0	47.4
No. of cigarettes/day	22.9	22.0	21.4	23.7	22.9	22.8
> 30 years of smoking (%)	22.6	19.7	18.6	26.0	23.4	21.3
Sports > 1 time/week (%)	31.2	34.1	36.6	27.8	31.3	39.3
Vitamin user (%)	11.9	13.7	16.3	10.6	12.4	16.2
Women						
No. of subjects	6150	7113	8595	7637	9852	9219
No. of lung cancer cases	13	9	21	15	22	19
Mean age (years)	49.0	49.5	50.2	53.9	54.0	55.2
Mean BMI (kg/m^2)	24.2	24.1	24.0	24.2	24.0	24.0
Alcohol intake (%)						
Never drinker	76.9	77.5	76.3	79.2	79.6	79.9
Weekly drinker	10.7	10.8	12.1	10.7	10.7	11.0
Cigarette smoking (%)						
Ever smoker	9.1	7.6	6.3	8.9	6.3	6.5
Current smoker	7.1	5.6	4.8	7.9	5.3	5.4
Sports > 1 time/week (%)	15.9	21.1	24.9	19.4	24.4	32.0
Vitamin user (%)	16.2	18.6	19.4	12.4	14.8	20.3

tively. These lung cancer cases were classified as 198 adenocarcinomas (46.3%), 100 squamous cell carcinomas (23.4%), 49 small cell carcinomas (11.4%), 21 large cell carcinomas (4.9%), 6 other histological types (1.4%), and 54 cases of unknown histological type (12.6%).

Table 1 shows background information for Cohort I and Cohort II according to categories of vegetable consumption. In both cohorts, participants with higher vegetable intakes were generally somewhat older, were more physically active, were more likely to take vitamin supplements, and were less likely to smoke. Among those who did smoke, a higher vegetable intake was associated with a lower quantity of cigarettes smoked. Smoking rates in the cohorts were comparable to those reported for Japanese men and women [24]. No marked differences in background variants were observed between cohorts, nor were measurable differences in socio-economic status found (data not shown). The majority of participants in both two cohorts were asked to answer the food frequency questionnaire in same seasons (between February and March).

No significant overall association between vegetable and fruit consumption and incidence of lung cancer was found (Table 2). Compared with subjects who consumed low amounts of vegetables only, fruit only, or both vegetables and fruit, age-, area- and gender-adjusted RRs of lung cancer were approximately unity for middle and high consumption in both Cohorts, and multiple adjustments for age, gender, area, sports, frequency of alcohol intake, body mass index, vitamin supplement use, salted fish and meat, pickled vegetables, smoking status, smoking duration, and number of cigarettes per day did not appreciably change RR

Table 2. Adjusted relative risks (RRs) and 95% confidence intervals (95% CI) of lung cancer according to categories of vegetable and fruit consumption

	Consumption category		
	Low	Middle	High
Vegetables			
Total no. of cases	159	126	143
No. of subjects	31516	30079	31,689
Total person-years	246,557	235,969	249,204
Mean intake (g/day)			
Cohort I	73.2	139.4	234.0
Cohort II	12.3	34.0	98.0
RR, Cohort I	1.00	1.07 (0.74–1.55)	1.11 (0.77–1.61)
RR, Cohort II	1.00	0.90 (0.65–1.23)	0.97 (0.71–1.33)
RR, Combined cohorts	1.00	0.96 (0.76–1.23)	1.03 (0.81–1.30)
Fruit			
Total No. of cases	164	145	119
No. of subjects	30,564	31,486	31,234
Total person-years	239,301	247,050	245,380
Mean intake (g/day)			
Cohort I	31.6	95.5	210.9
Cohort II	14.4	55.2	138.4
RR, Cohort I	1.00	1.41 (0.99–2.02)	1.40 (0.92–2.13)
RR, Cohort II	1.00	0.83 (0.62–1.13)	1.01 (0.72–1.41)
RR, Combined cohorts	1.00	1.08 (0.64–1.81)*	1.16 (0.84–1.58)
Vegetables + fruit			
Total No. of cases	161	137	130
No. of subjects	31123	31062	31099
Total person-years	243841	244434	243456
Mean intake (g/day)			
Cohort I	127.8	243.8	418.2
Cohort II	36.7	94.9	220.6
RR, Cohort I	1.00	0.99 (0.68–1.45)	1.31 (0.90–1.92)
RR, Cohort II	1.00	0.95 (0.70–1.29)	0.94 (0.68–1.31)
RR, Combined cohorts	1.00	0.97 (0.76–1.23)	1.10 (0.79–1.52)

* $p = 0.03$ in test for heterogeneity; RRs adjusted for age, gender, areas, sports, frequency of alcohol intake, body mass index, vitamin supplement use, salted fish and meat, pickled vegetables, smoking status, smoking duration, and number of cigarettes per day.

estimates. Due to different numbers of items and different kinds of vegetables and fruit included in the food frequency questionnaires across the two cohorts, vegetable and fruit consumption in Cohort I was about two- or three-fold higher than in Cohort II. Despite differences in estimated intakes between the two cohorts, no significant association was observed between consumption of vegetables and fruit and lung cancer in either Cohort I or Cohort II. Similarly, the p-value for heterogeneity exceeded 0.05 for most food groups except for the middle intake category of fruit, indicating the absence of significant heterogeneity in results across the two studies.

Due to the powerful influence of smoking on incidence of lung cancer and the correlations between many smoking characteristics and diet, smoking represents a strong confounder in associations between vegetable and fruit consumption and risk of lung cancer. We therefore stratified smoking status into never and ever-smokers (Table 3). Data were combined because most RR estimates from Cohorts I and II did not show significant heterogeneity (at $p < 0.05$). No significant association between vegetables and fruit and risk of lung cancer was found among either never smokers or ever smokers.

The absence of a relationship between fruit and vegetable consumption and lung cancer incidence was consistent across strata of histological type (Table 4). Relative risks of high consumption of vegetables only, fruit only, and vegetables and fruit for non-adenocarcinoma was 0.79 (95% CI 0.55–1.16), 0.96(95% CI 0.62–1.49), and 0.85 (95% CI 0.60–1.25) respectively compared to low consumption group. Total vegetables and fruit consumption appeared more protective for non-adenocarcinoma tumors than for adenocarcinoma. Risk estimates for middle and high intakes of vegetables only, fruit only, and vegetables and fruit combined were all below one for non-adenocarcinoma and above one for adenocarcinoma, although these results were not significant and no clear linear trend was observed. When the two cohorts were calculated separately, similar patterns of results were found for the two cohorts (data not shown). In addition, inverse associations between lung cancer and specific individual vegetables and fruit such as tomato, carrot, citrus, and apple were not observed in Cohort II (data not shown).

Table 3. Combined relative risks (RRs) and 95% confidence intervals (95% CI) of lung cancer according to categories of vegetable and fruit consumption among smokers and non-smokers

	Never smokers			p Value for trend	Ever smokers			p Value for trend
	Low	Middle	High		Low	Middle	High	
Vegetables								
Cases	28	31	47		129	94	94	
No. of subjects	16481	19182	20386		15180	10983	11389	
Person-years	130452	150722	162604		116899	85756	87092	
RR^1	1.00	0.96 (0.37–2.45)	1.37 (0.79–2.37)	0.20	1.00	0.94 (0.62–1.43)	0.90 (0.69–1.17)	0.41
RR^2					1.00	1.02 (0.69–1.50)	0.97 (0.71–1.34)	0.80
Fruit								
Cases	25	26	55		136	119	62	
No. of subjects	14185	18010	23854		16517	13582	7453	
Person-years	110627	143425	189726		129494	104202	56052	
RR^1	1.00	1.17 (0.25–5.48)	2.09 (0.56–7.83)	0.22	1.00	1.01 (0.64–1.61)	0.85 (0.63–1.15)	0.42
RR^2					1.00	1.13 (0.78–1.63)	1.00 (0.72–1.38)	0.78
Vegetables + fruit								
Cases	24	32	50		136	102	79	
No. of subjects	15309	18835	21905		15952	12320	9280	
Person-years	121244	149661	172873		123386	95310	71052	
RR^1	1.00	1.34 (0.52–3.42)	1.95 (0.84–4.52)	0.17	1.00	0.92 (0.71–1.19)	0.86 (0.64–1.15)	0.27
RR^2					1.00	0.93 (0.69–1.27)	1.01 (0.72–1.40)	0.97

RR^1: Adjusted for age, gender, area, sports, frequency of alcohol intake, body mass index, vitamin supplement use, salted fish and meat, and pickled vegetables; RR^2: Adjusted for covariate in RR^1, smoking duration, and number of cigarettes per day among ever smokers.

Table 4. Combined relative risks (RRs) and 95% confidence intervals (95% CI) of lung cancer by histological classification according to categories of vegetable and fruit consumption

	Adenocarcinoma			Non-adenocarcinoma		
	Number	RR^1	RR^2	Number	RR^1	RR^2
Vegetables						
Low	62	1.00	1.00	77	1.00	1.00
Middle	65	1.18 (0.83–1.68)	1.25 (0.70–2.23)	48	0.76 (0.53–1.09)	0.80 (0.55–1.16)
High	71	1.17 (0.83–1.66)	1.13 (0.66–1.94)	51	0.75 (0.52–1.07)	0.79 (0.55–1.16)
p Value for trend		0.48	0.24		0.09	0.21
Fruit						
Low	67	1.00	1.00	79	1.00	1.00
Middle	70	1.27 (0.58–2.80)	Cohort I: 2.06 (1.20–3.54)* Cohort II: 0.88 (0.56–1.39)*	51	0.67 (0.43–1.04)	0.76 (0.46–1.24)
High	61	1.30 (0.79–2.12)	1.40 (0.79–2.48)	46	0.83 (0.57–1.22)	0.96 (0.62–1.49)
p Value for trend		0.45	0.27		0.24	0.99
Vegetables+fruit						
Low	68	1.00	1.00	76	1.00	1.00
Middle	64	1.00 (0.71–1.42)	1.01 (0.61–1.67)	55	0.78 (0.55–1.10)	0.81 (0.57–1.17)
High	66	1.12 (0.71–1.75)	1.02 (0.56–1.87)	45	0.72 (0.49–1.04)	0.85 (0.57–1.25)
p Value for trend		0.61	0.33		0.05	0.35

* $p = 0.02$ in test for heterogeneity.

RR^1:Adjusted for age, gender, area, sports, frequency of alcohol intake, body mass index, vitamin supplement use, salted fish and meat, and pickled vegetables; RR^2: Adjusted for covariate in RR^1, smoking status, smoking duration, and number of cigarettes per day among ever smokers.

Multiple-adjustments for sports, frequency of alcohol intake, body mass index, vitamin supplement use, salted fish and meat, and pickled vegetables did not influence estimates from age-, area-, and gender-adjusted RR of lung cancer. Additional adjustment for energy intake and passive smoking again did not modify the result (data not shown). Further adjustment for smoking status, smoking duration, and number of cigarettes per day among ever smokers slightly changed RRs but did not alter interpretations of results in the final analysis. In addition, we categorized vegetable-only, fruit-only and total vegetable and fruit intakes into six groups, and investigated whether any effect existed for very high vegetable and fruit intake. RRs for the uppermost versus lowermost sixths of consumption were around unity. Findings of the present study did not differ when analyses were limited to men (data not shown).

Discussion

We did not observe among either Cohort I or Cohort II any lower risk of lung cancer with higher fruit and/or vegetable intake. In addition, there was no clear evidence of a decrease in risk when results from the two cohorts were combined. The association between vegetables and fruit consumption and risk of lung cancer did not vary substantially according to smoking status or histological subtypes of cancer. Our study yielded results that challenge widely held beliefs, since vegetable and fruit consumption is currently considered to offer a convincing protective benefit against lung cancer [25].

Discrepancies between the results of our study and most previous studies showing inverse associations between vegetable and fruit intake are likely attributable, at least in part, to inadequate control for smoking status. Some previous studies controlled only for smoking status and drew conclusions suggesting lower risk of lung cancer [26, 27]. Given the powerful influence of smoking on incidence of lung cancer, insufficient control for smoking may overestimate the benefits of vegetable and fruit intakes [16, 28]. Discrepancies in study results may also be explained by numbers of never versus current smokers in the study population. Although adjustment for smoking status, smoking duration, and number of cigarette per day did not significantly change the results of our study, the magnitude of confounding in smoking-related variables might be greater in populations of some previous studies than in the populations of the present study.

Although in many previous studies multiple fruit and vegetables or groups of these foods were considered,

often only one food or food group emerged as inversely related to incidence of lung cancer. In a Swedish study, only carrot consumption displayed an inverse association with risk of lung cancer, albeit non-significantly [15]. As such studies in which only one or two food groups displayed a protective effect were usually considered as 'positive' studies, the overall protective effect of vegetable and fruit intake on lung cancer has probably been overstated. In addition, the findings are controversial in subgroups of study population among studies. Many studies have indicated a clear protective effect of fruit and vegetables only among current smokers [9–12], while others have suggested stronger protective effects among never or past smokers rather than current smokers [13–15]. The controversial results of studies regarding smoking status may raise suspicion regarding the inverse association of vegetable and fruit intake with lung cancer.

Besides smoking, frequent consumption of fruit and vegetables is associated with a number of other predictors of lung cancer, such as high physical activity, high use of vitamin supplements, and lower intake of fat. Confounding by measured and unmeasured factors is of considerable concern in studies of diet and disease. Many of these potential confounders for lung cancer have not been appreciated or measured until recently. Some previous studies that have found apparent protective effects from high intakes of fruit and vegetables may thus have been confounded by other lifestyle factors. While we did not find that any of the potential confounders considered in our adjusted analyses appreciably altered our estimates, the degree of confounding might be greater in populations that are more heterogeneous in areas of residence and occupation than the populations from rural areas of Japan in the present study.

The majority of studies have found a reduced risk of lung cancer associated with intake of both fruit and vegetables, but prospective studies, which avoid recall and selection biases, have provided weaker evidence than case–control studies. Like the present study, results of several prospective studies have cast some doubt on whether vegetables and fruit are associated with reductions in risk of lung cancer. Neither an American cohort study [8] nor a Japanese cohort study [26] observed any inverse association between intake of vegetables and fruit and lung cancer risk. A recent report on two large cohorts of health workers in the USA did not observe a decreased risk among men, although a non-significant trend toward reduced risk was found among women [16]. In addition, serum micronutrient studies, which avoid the problems of inaccurate accounting of diet or recall bias, have also generally found no significant relationships with any micronutrient other than carotenoids [29]. Moreover, intervention trials with ingestion of β-carotene and vitamin A/E supplements have repeatedly induced excess lung cancers. The Finnish ATBC cancer prevention study found a significant 18% higher incidence of lung cancer among male smokers who took 20 mg of β-carotene daily [30]. Another trial (CARET) in the USA found that subjects taking 30 mg of β-carotene and 25,000 IU of vitamin A for about four years displayed 28% greater incidence of lung cancer [31]. Furthermore, as indicated by Koo, social health-consciousness in a particular period influencing studies and health beliefs about the benefits of vegetable and fruit consumption may also account for some of the inverse associations [29].

If diet plays an important role in lung cancer, such effects may well occur in the earlier stages of development, such as adolescence or even preschool age. Along with the Westernization of diets in Japan during the previous decades, diets may differ between youth and adulthood. Consumption of green-yellow vegetables increased from 49.0 to 72.8 g per capita from 1965 to 1988 in Japan [32]. As suggested by the Zutphen Study, in which consistently high intakes of fruit and vegetables on three assessments over a 10-year period before follow-up showed a much stronger association with risk of lung cancer than any one individual measure [33], longer lag time between diet measurement and disease diagnosis, and repeated dietary measures permitting consideration of both distant and more proximate dietary intakes are needed to reduce measurement error.

As indicated previously, reported fruit and vegetable consumption increases with the number of fruit and vegetables items on the questionnaire [34]. Fruit and vegetable intake may thus be underestimated by one-month diet records if they did not capture full seasonal variation in consumption. The majority of participants answered questionnaires between February and March, meaning that diet between January and February was measured. Some fruits and vegetables like citrus fruits and carrots are widely available, while others like strawberries and tomatoes are not common, although most fruit and vegetables can be bought throughout the year thanks to advances transportation systems and hothouse technology in Japan. An investigation into seasonal variation by the JPHC study into fruit and vegetable consumption has indicated that, for most nutrients, seasonal misclassification of usual intake is small except for vitamin C, which might be consumed less in winter than in other seasons [35]. The possibility that diet for a one-month period in a year may not represent long-term habitual diet, which may be more relevant to cancer risk, cannot be completely ruled out. In our validation study, the mean daily total vegetable

intake of 271.8 g was estimated from diet records in Cohort I, against only 132.9 g from the questionnaire in the same subjects. This underestimation might misclassify estimates of fruit and vegetable consumption through use of a simple food frequency questionnaire, and might lower rank correlations between reported consumption and real intake, which makes it difficult to find if inverse associations actually exist.

Interactions among nutritional components are complex, and it is unclear when dietary components are most effective in relation to the onset of disease. Some studies have shown that total vegetable and fruit consumption are related to decreased risk, while others have found specific individual foods account for the protective effect. Therefore, in Cohort I we examined the role of total vegetables and fruit, then in Cohort II, we examined representative kinds of vegetables and fruit which were the most interesting and have been frequently indicated to be primarily responsible for lower risk of lung cancer in previous studies, including green vegetables, and individual vegetables and fruit high in vitamin C (citrus) [12], lycopene (tomato) [14], α- or β-carotene (carrot) [13, 33], and catechin (apple) [36, 37]. However, inverse associations were observed in neither general total vegetable and fruit consumption nor several individual vegetables and fruit.

Vegetables and fruit are considered to play a more beneficial role for non-adenocarcinoma lung cancer than for adenocarcinoma [12, 14, 18]. The present study is inconsistent with this notion, instead suggesting that risk estimates for middle and high intakes of vegetables only, fruit only, and vegetables and fruit combined were all below 1 for non-adenocarcinoma and above 1 for adenocarcinoma, although no statistically significant differences were noted.

In conclusion, contrary to widely held beliefs, the results of our large Japanese cohorts suggest that fruit and vegetable consumption during adulthood is not significantly associated with development of lung cancer.

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Members of the Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases (JPHC Study) Group are: S. Tsugane, T. Hanaoka, T. Sobue, M. Inoue, National Cancer Center Research Institute, Kashiwa and Tokyo; J. Ogata, S. Baba, T. Mannami, National Cardiovascular Center, Suita; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, I. Hashimoto, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Nagano Prefectural Saku Public Health Center, Saku; Y. Kishimoto, E. Takara, T. Fukuyama, M. Kinjo, M. Irei, Okinawa Prefectural Chubu Public Health Center, Ishikawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Mito; K. Matsui, T. Abe, Niigata Prefectural Kashiwazaki Public Health Center, Kashiwazaki; M. Doi, A. Terao, Y. Ishikawa, Kochi Prefectural Chuo-higashi Public Health Center, Tosayamada; H. Sueta, H. Doi, M. Urata, N. Okamoto, F. Ide, Nagasaki Prefectural Kamigoto Public Health Center, Arikawa; H. Sakiyama, N. Onga, H. Takaesu, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, M. Ichii, Osaka Prefectural Suita Public Health Center, Suita; S. Matsushima, S. Natsukawa, Saku General Hospital, Usuda; S. Watanabe, M. Akabane, Tokyo University of Agriculture, Tokyo; M. Konishi, K. Okada, Ehime University, Matsuyama; H. Iso, Y. Honda, Tsukuba University, Tsukuba; H. Sugimura, Hamamatsu University, Hamamatsu; Y. Tsubono, Tohoku University, Sendai; M. Kabuto, National Institute for Environmental Studies, Tsukuba; S. Tominaga, Aichi Cancer Center Research Institute, Nagoya; M. Iida, W. Ajiki, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, Kochi Medical School, Nankoku; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; the late M. Yamaguchi, Y. Matsumura, S. Sasaki, National Institute of Health and Nutrition, Tokyo; and T. Kadowaki, Tokyo University, Tokyo.

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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

Manami Inoue, M.D.,[a,*] Tomoyuki Hanaoka, M.D.,[a] Sizuka Sasazuki, M.D.,[a] Tomotaka Sobue, M.D.,[b] Shoichiro Tsugane, M.D.,[a] and for the JPHC Study Group[1]

[a] *Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 104-0045 Tokyo, Japan*
[b] *Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 104-0045 Tokyo, Japan*

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

* Corresponding author. Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Fax: +81-3-3547-8578.
E-mail address: mnminoue@gan2.res.ncc.go.jp (M. Inoue).
[1] Study group members were listed in the Acknowledgments at the end of this article.

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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

Table 2
Hazard ratios of cancer incidence and death according to smoking status in men[a]

	Person-years of follow-up	Total cancer incidence (n = 2,969)			Total cancer death (n = 1,411)		
		Number of cases	Hazard ratio	95% CI	Number of cases	Hazard ratio	95% CI
Smoking status							
Never	103,566.91	488	1.00	(reference)	223	1.00	(reference)
Former	97,228.66	777	1.37	(1.22–1.54)	351	1.35	(1.13–1.53)
Current	217,856.57	1704	1.64	(1.48–1.82)	837	1.78	(1.53–2.09)
Daily cigarette consumption							
≤19	57,531.54	483	1.48	(1.29–1.68)	244	1.64	(1.35–1.98)
20–29	96,331.55	796	1.71	(1.52–1.93)	391	1.86	(1.56–2.21)
≥30	63,993.48	425	1.72	(1.51–1.98)	202	1.84	(1.51–2.25)
trend			$P < 0.05$			n.s.	
Pack-years							
≤19	38,586.82	190	1.26	(1.06–1.49)	96	1.49	(1.16–1.91)
20–29	55,219.95	307	1.54	(1.33–1.79)	153	1.75	(1.41–2.17)
30–39	53,375.19	474	1.76	(1.54–2.08)	220	1.86	(1.53–2.26)
≥40	70,523.45	732	1.76	(1.56–1.98)	367	1.86	(1.56–2.22)
trend			$P < 0.001$			n.s.	
Age started smoking							
≥25	33,441.41	283	1.50	(1.28–1.74)	142	1.65	(1.32–2.06)
20–24	129,048.02	1001	1.62	(1.45–1.82)	473	1.71	(1.45–2.03)
≤19	55,367.14	420	1.81	(1.58–2.08)	222	2.11	(1.73–2.57)
trend			$P < 0.05$			$P < 0.05$	

[a] Adjusted for years of age at baseline (continuous), study area (categorical), weekly ethanol intake (no, occasional, <150 g, 150–299 g, 300–449 g, ≥450 g), 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).

increased risk (HR 1.03; 95% CI 0.53–1.99), and only current smokers increased the risk (HR 1.58; 95% CI 1.18–2.12). No significant increasing or decreasing risk trend was observed according to the daily and pack-year cigarette consumption and age started smoking in women, for both total cancer incidence and death.

Table 3
Hazard ratios and of cancer incidence and death according to smoking status in women[a]

	Person-years of follow-up	Total cancer incidence (n = 1,953)			Total cancer death (n = 721)		
		Number of cases	Hazard ratio	95% CI	Number of cases	Hazard ratio	95% CI
Smoking status							
Never	436,948.22	1779	1.00	(reference)	656	1.00	(reference)
Former	6352.38	37	1.47	(1.05–2.05)	10	1.03	(0.53–1.99)
Current	26,117.26	137	1.46	(1.21–1.75)	55	1.58	(1.18–2.12)
Daily cigarette consumption							
≤19	16,566.89	90	1.45	(1.16–1.81)	32	1.36	(0.93–2.00)
20–29	6707.38	32	1.42	(0.99–2.03)	16	1.99	(1.20–3.31)
≥30	2842.99	15	1.63	(0.98–2.72)	7	1.96	(0.93–4.15)
trend			n.s.			n.s.	
Pack-years							
≤19	16,835.45	80	1.34	(1.06–1.69)	23	1.08	(0.69–1.67)
20–29	4503.64	30	1.78	(1.20–2.63)	20	3.37	(2.09–5.44)
30–39	1965.21	10	1.32	(0.71–2.47)	7	2.18	(1.03–4.62)
≥40	2788.12	17	1.83	(1.13–2.96)	5	1.26	(0.52–3.06)
trend			n.s.			n.s.	
Age started smoking							
≥25	17,269.16	92	1.39	(1.12–1.73)	35	1.41	(0.99–2.00)
20–24	7223.20	40	1.73	(1.24–2.41)	18	2.22	(1.34–3.70)
≤19	1624.90	5	1.10	(0.45–2.66)	2	1.36	(0.34–5.51)
trend			n.s.			n.s	

[a] Adjusted for years of age at baseline (continuous), study area (categorical), weekly ethanol intake (no, monthly, <100 g, ≥100 g), 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).

The positive fraction attributable to exposure to smoking habit among cancer cases in the male population was also estimated. In men, 22.4% (95% CI 15.7–28.5) of cancer occurring in the study period was due to current exposure, 7.0% (95% CI 3.7–10.3) to past exposure, and 26.1% (95% CI 15.6–35.2) of the cancer deaths was due to current exposure and 6.5% (95% CI 1.6–11.0) to past exposure. Thus, these cases were considered to have been preventable by avoidance of smoking. In women, in contrast, only 2.2% (95% CI 0.6–3.7) of cancer incidence and 2.7% (95% CI 0.0–5.5) of the cancer deaths were attributable to current exposure to smoking, probably since the prevalence of smoking was very low in this population.

Additionally, when men and women were combined, 37.4% of the study subjects currently smoked and 16.5% had quit smoking. Increased HR for total cancer incidence was 1.61 for current smokers and 1.43 for former-smokers. When males and females were combined, we estimated that 14.2% of the cancer occurring in the study period was attributable to current exposure and 5.0% to past exposure. These cases were considered to have been preventable by avoidance of smoking.

Discussion

Although the harmful effects of tobacco smoking on cancer at various sites have been unequivocally established, few studies have targeted the subsequent risk and population attributable fraction of total cancer incidence. Existing evidences using a Japanese population have been limited to the analysis of cancer mortality [6–11] and to the incidence of cancer at specific sites [20–25], if any. Both in men and women, our results on cancer deaths showed a relative risk higher than those of previous reports on mortality using a Japanese population. The relative risk of current smokers on all cancer deaths in these reports was 1.5–1.7 in men. In women, our current results on cancer deaths showed a slightly higher risk (HR 1.6) than the 1.1–1.3 reported by other investigators. Cancers weakly associated with tobacco smoke such as breast cancer have a better prognosis. In the analysis targeted on cancer deaths in no more than 10 years of follow-up, the fraction of these cancers was smaller than for smoking-related cancers that have a relatively poor prognosis such as lung cancer. Since the follow-up period of our study on cancer incidence was also nearly 10 years, it is still possible that the longer-term effects of smoking on cancer incidence remain to be seen.

It has long been acknowledged that the risk estimates of smoking-related cancers due to smoking habit are lower in Japan than in Western populations [23]. Focusing on total cancer mortality, the risk estimates of current smokers for all cancer deaths were more than two times higher among U.S. veterans [26] and among British males [27]. PAF was also discussed in several studies, in which the PAF of German current smokers is 39% in men and 12% in women, with the prevalence of current smokers at 33% and 18%, respectively [28]. Reports on cancer mortality from other Asian populations show a smoking-related association somewhat similar to that in the Japanese population, probably due to the high prevalence of male smokers and the low prevalence of female smokers in these Asian countries. The relative risk was 1.3 and 1.1 for Korean male and female smokers, and the corresponding PAF was 17% and 2%, respectively [29]. In Taiwan, the relative risk was 1.5 and 1.7 for Chinese male and female current smokers, and the corresponding PAF was 21% and 3% [30], respectively.

The relatively low-dose exposure to tobacco smoking especially among Japanese compared with Western countries due to the relatively late increase in tobacco consumption in Japan after 1950 and less chance to start smoking in their adolescence would partly contribute to this modest increase in risk [10,19,31]. The influence of passive smoking from family members as well as from the general environment also cannot be ignored. By contrast with the relatively low-dose exposure to tobacco smoking in Japan in the past, the prevalence of male current and former smokers is higher than in Western countries. Therefore, never-smokers in Japan are likely to be exposed to passive smoking environment given this high prevalence of male current and former-smokers. This would lead to underestimation of the true risk of smoking if the effect of passive smoking exists, since subjects with passive smoking are included in nonexposed groups. In the present analysis, we could not fully evaluate the effect of passive smoking due to the lack of detailed information, and this is a limitation of our study. Genetic susceptibility to tobacco smoke may also contribute to this risk difference, which has been indicated by ethnic comparison [32] and gene–environment interaction [33,34], while site specificity should be further investigated.

The major strength of the present study is its prospective design. Information on smoking habits was collected before subsequent diagnosis of cancer, which precludes the exposure recall bias inherent in case-control studies. Possible misclassification of the smoking status should also be considered, and the influence of modification in smoking behavior during the study period cannot be ignored. Smoking cessation after the baseline study due to some symptoms related to subsequent cancer may lead to underestimation of the true risk among current smokers who continue to smoke. Likewise, the risk of past smokers would be overestimated if this category includes subjects who resumed smoking.

Study subjects were selected from the general population, and the response rate of 82% to the baseline questionnaire would be acceptable in such a study setting. The proportion of losses to follow-up (0.05%) was negligible during the study period.

Although the quality of the cancer registry system was satisfactory over the study period, there was geographical variation by study area. In our study, we adjusted the study areas in the analysis to control such geographical variation. We confirmed in the present study that the quality was not

affected by smoking status at baseline, and therefore, possible misclassification of the cancer occurrence by underreporting of cancer diagnosis would be nondifferential and would lead to underestimation of the results.

Since two metropolitan areas were excluded from the present analysis due to different definitions of the study population, our result may not be generalized straight to the urban Japanese population, which is another limitation of the present study. Especially in women, the proportion of current smokers was 12–20% in these two metropolitan areas. This is very high compared with the 4–10% proportion in the area included in the analysis. A relatively low proportion of smokers may have underestimated the PAF of tobacco smoke.

While allowing for these methodological issues, the present analysis provides practical information on the impact of tobacco smoke on Japanese cancer incidence. In our study population in which 52% were male current smokers, it was estimated that 29% of cancer occurrence would have been preventable had all male smokers avoided tobacco smoking. In women, since the proportion of smokers was no more than 6%, only a 3% cancer incidence was preventable by avoidance of tobacco smoking. If we apply the prevalence of current and former smokers in the general Japanese population (men: current 45.9%, former 27.5%; women: current 9.9%, former 3.2%) [35], the latest estimates of total cancer incidence in Japan by population-based cancer registries (men: 275,300 cases; women: 203,900 cases in 1997) [36], and the HR estimated in the present study, PAF for ever-smoking is estimated to be 28.6% in men and 4.1% in women. Accordingly, roughly 78,800 male and 8,400 female incident cancer cases would be preventable by avoidance of tobacco smoking. The results of this study have important ramifications for policy makers and the public health sector in charge of formulating specific tobacco control measures for the Japanese population.

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Members of the Japan Public Health Center-based Prospective Cohort Study on Cancer and Cardiovascular Diseases (JPHC Study) Group: S Tsugane, T Sobue, T Hanaoka, M Inoue, National Cancer Center Research Institute; J Ogata, S Baba, T Mannami, National Cardiovascular Center; K Miyakawa, F Saito, A Koizumi, Y Sano, I Hashimoto, Iwate Prefectural Ninohe Public Health Center; Y Miyajima, N Suzuki, S Nagasawa, Y Furusugi, Akita Prefectural Yokote Public Health Center; H Sanada, Y Hatayama, F Kobayashi, H Uchino, Y Shirai, T Kondo, R Sasaki, Y Watanabe, Nagano Prefectural Saku Public Health Center; Y Kishimoto, E Tanaka, M Kinjo, T Fukuyama, M Irei, Okinawa Prefectural Chubu Public Health Center; K Imoto, H Yazawa, T Seo, A Seiko, F Ito, Katsushika Public Health Center; A Murata, K Minato, K Motegi, T Fujieda, Ibaraki Prefectural Mito Public Health Center; K Matsui, T Abe, Niigata Prefectural Kashiwazaki Public Health Center; M Doi, Y Ishikawa, A Terao, Kochi Prefectural Chuo-higashi Public Health Center; H Sueta, H Doi, M Urata, Nagasaki Prefectural Kamigoto Public Health Center; H Sakiyama, N Onga, H Takaesu, Okinawa Prefectural Miyako Public Health Center; F Horii, I Asano, H Yamaguchi, K Aoki, S Maruyama, M Ichii, Osaka Prefectural Suita Public Health Center; S Matsushima, S Natsukawa, Saku General Hospital; S Watanabe, M Akabane, Tokyo University of Agriculture; M Konishi, K Okada, Ehime University; H Iso, Y Honda, Tsukuba University; H Sugimura, Hamamatsu University School of Medicine; Y Tsubono, Tohoku University; N Kabuto, National Institute for Environmental Studies; S Tominaga, Aichi Cancer Center; M Iida, W Ajiki, Osaka Medical Center for Cancer and Cardiovascular Disease; S Sato, Osaka Medical Center for Health Science and Promotion; N Yasuda, Kochi Medical School; S Kono, Kyushu University; K Suzuki, Research Institute for Brain and Blood Vessels Akita; Y Takashima, Kyorin University; E Maruyama, Kobe University; M Yamaguchi, Y Matsumura, S Sasaki, National Institute of Health and Nutrition.

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

Mi Kyung KIM[1,2], Satoshi SASAKI[1,3], Shizuka SASAZUKI[1] and Shoichiro TSUGANE[1]*
for the Japan Public Health Center-based Prospective Study Group

[1]*Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan*
[2]*Department of Preventive Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea*
[3]*National Institute of Health and Nutrition, Tokyo, Japan*

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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*Correspondence to: Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Fax: +81-3-3547-8578. E-mail: stsugane@ncc.go.jp

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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.