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.

Acknowledgments

The authors thank all staff members in each study area for their unfailing efforts to conduct the baseline and follow-up surveys. Gratitude is hereby expressed to the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki and Okinawa Cancer Registries for providing the incidence data. The authors are also indebted to Drs. S Watanabe and M Konishi who contributed to the initiation of the JPHC study and to Mss. Y Iwatare, M Takahashi, M Hosokawa, M Izuka, M Konishi and K Ohashi for their technical assistance.

This work was supported by the Grant-in-Aid for Cancer Research and for the Second Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare, Japan.

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Cancer Causes and Control **15**: 349–357, 2004.
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Vegetables, fruit consumption and risk of lung cancer among middle-aged Japanese men and women: JPHC study

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Received 15 December 2003; accepted in revised form 12 February 2004

Key words: lung cancer, non-adenocarcinoma, prospective study, smoking, vegetable and fruit consumption.

Abstract

Objective: To investigate the association between vegetable and fruit consumption and incidence of lung cancer.
Methods: Self-administered questionnaires were used to assess diet in two large population-based cohorts with 42,224 and 51,114 subjects in 1990 and 1993, respectively. After ten and seven years of follow-up, we ascertained 428 newly diagnosed case of lung cancer. Relative risk (RR) estimates were calculated using the Cox proportional hazards model with pooling of estimates from the two cohorts.
Results: Total vegetable and fruit intake was not associated with lowered risk of lung cancer, with RR approximating unity. The null relation between vegetable and fruit consumption and lung cancer incidence was consistent across strata of smoking status (never or ever smokers). When dividing lung cancers into adenocarcinoma and non-adenocarcinoma, risk 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 no statistically significant differences were noted. Similar patterns of results were found when the two cohorts were analyzed separately.
Conclusions: Contrary to popular belief, our results suggest that vegetables and fruit do not appear to confer protection from lung cancer.

Introduction

Numerous studies have indicated that diets high in fruit and vegetables are associated with a lower risk of lung cancer [1–5], although a minority of studies have expressed a different opinion [6–8]. However, findings are controversial in subgroups of study populations between studies. Many studies have indicated a clear protective effect of fruit and vegetables only among current smokers [9–12], and have concluded that antioxidants from vegetables and fruit strongly reduce oxidative stress due to smoking. Conversely, others have found a stronger protective effect among non-smokers [13–16], and have argued that the inverse association among smokers found by some studies might be confounded by unmeasured smoking characteristics. Furthermore, although some Western studies have reported that fruit and vegetables play a more beneficial role for non-adenocarcinoma than for adenocarcinoma [14, 17, 18], information on this issue in Asian countries is scarce and based on case–control studies [19]. No previous cohort study has investigated the influence of vegetable and fruit intake on lung cancer by histological types in Japan. We prospectively investigated the association between vegetable and fruit consumption and incidence of lung cancer in two large population-based cohorts in Japan, where the role of cigarette smoking is less significant than in Western countries. The study expected to reveal whether an inverse association of vegetables and fruit with lung cancer exists and whether the association differs by smoking status and histological type.

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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.

Acknowledgements

This study was supported by grants-in-aid for cancer research and for the Second-Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health and Welfare of Japan. Dr. Y. Liu received a Research Resident Fellowship from the Foundation for Promotion of Cancer Research (Japan) for the 2nd Term Comprehensive 10-Year-Strategy for Cancer Control.

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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Cancer Causes and Control **15**: 483–491, 2004.
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Green tea consumption and subsequent risk of gastric cancer by subsite: the JPHC Study☆

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Received 21 July 2003; accepted in revised form 1 March 2004

Key words: gastric cancer, green tea, prospective study.

Abstract

Objective: To investigate the relationship between green tea consumption and subsequent risk of gastric cancer at different anatomical subsites in a population-based prospective study.
Methods: The Japan Public Health Center-based prospective study (JPHC Study) was established in 1990 for Cohort I and in 1993 for Cohort II. Among 72,943 subjects (34,832 men and 38,111 women), 892 gastric cancer cases (665 men and 227 women) were identified from 1990 to 2001.
Results: While no association between green tea consumption and gastric cancer was observed among men, a decreased risk of gastric cancer was observed among women after adjustment for potential confounding factors. This result was more remarkable when only the tumors in the distal portion were analyzed; for that subsite, the relative risk was 0.51 (95% confidence interval 0.30–0.86) in the highest category of green tea consumption (5 or more cups per day *versus* less than 1 cup per day) (p for trend = 0.01). The null association for upper-third gastric cancer was consistent for both sexes.
Conclusions: An inverse association between green tea consumption and distal gastric cancer was observed among women. More prospective studies with detailed information are needed to confirm the role of green tea in the occurrence of gastric cancer.

Introduction

Gastric cancer is one of the cancers known to have its risk modified primarily by dietary factors. Accumulated evidence shows that a reduction in salty food intake and an increase in vegetable and fruit intake are important in the primary prevention of gastric cancer [1].

A possible protective effect of green tea on gastric cancer has also been suggested. Antioxidant activities and the ability to inhibit nitrosation of polyphenols have been isolated from green tea in both *in vitro* and *in vivo* studies [2–4]. In contrast with the *in vivo* studies and the majority of case-control studies that have provided evidence for a protective effect of green tea against gastric cancer [5], recent prospective studies have not shown any association between green tea consumption and gastric cancer risk [6–8]. Although not statistically significant, a decreased risk was suggested for women in two of the studies [6, 8] and additional data from prospective studies are strongly needed. To clarify this relationship, we analyzed the data from a population-based prospective cohort study conducted in Japan, where green tea is commonly consumed.

Previous studies have also demonstrated that gastric cancer cannot be explained as a single entity [9]. In

☆ This work was supported by the Grant-in-Aid for Cancer Research and for the Second Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan. Shizuka Sasazuki is an Awardee of a Research Resident Fellowship from the Foundation for Promotion of Cancer Research in Japan.

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contrast to the decline in the occurrence of distal gastric cancers [10], recent reports have revealed that the incidence of cancer localized to the cardia may be on the rise [11, 12]. The observed differences in clinical and pathologic profiles suggest that these two tumors are distinct diseases with different etiologies [13]. This is the first study to prospectively analyze the relationship considering the anatomical subsites of the tumors.

Materials and methods

Study population

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) was established in 1990 for Cohort I and in 1993 for Cohort II, which has been partially reported on elsewhere [14, 15]. Cohort I, consisting of three Public Health Center (PHC) areas (Ninohe PHC area of Iwate prefecture, Yokote PHC area of Akita prefecture, and Saku PHC area of Nagano prefecture), and Cohort II, consisting of four PHC areas (Mito PHC area of Ibaraki prefecture, Kashiwazaki PHC of Niigata prefecture, Chuo-higashi PHC of Kochi prefecture, and Kamigoto PHC of Nagasaki prefecture) were used in the present analysis. The study population was defined to be all inhabitants in the study areas (23 cities, towns, or villages in 7 PHCs) aged 40–59 years in Cohort I and aged 40–69 years in Cohort II at the baseline of the survey. We did not include the Ishikawa PHC area and the Miyako PHC area in the Okinawa prefecture. According to our previous report [16, 17], the distribution of risk factors including smoking habits and dietary factors in Okinawa were quite different from those of other PHC areas, which in turn made us unable to adjust these factors simultaneously to the other areas. Cohort I and Cohort II also contained subjects from the Katsushika PHC of Tokyo prefecture and Suita PHC of Osaka prefecture, respectively, who took part in a health check-up program at age 40 and 50 during 1990–1994 for Katsushika PHC and 1993–1994 for Suita PHC. We did not include these subjects because the selection of subjects was different from that of other PHC areas and cancer incidence was not monitored in the Katsushika PHC area. Consequently, the background of the study subjects were quite different and there was no overlap with the recent cohort studies in Japan on green tea and gastric cancer whose subjects were drawn from residents in three municipalities of Miyagi Prefecture [6], or bomb survivors who have been under continued surveillance [7], or participants of general health check ups of 45 municipalities [8].

As a whole, a population-based cohort of 43,322 men (19,753 in Cohort I and 23,569 in Cohort II) and 45,258 women (20,539 in Cohort I and 24,719 in Cohort II) was established.

Baseline questionnaire

Subjects were asked to reply to a lifestyle questionnaire, covering sociodemographic characteristics, medical history, and diet, as well as drinking habits for green tea, black tea, and coffee. The survey was conducted in 1990 for Cohort I and in 1993 for Cohort II (with the exception of Tomobe town, with 12,463 subjects, which belongs to Mito PHC in Cohort II, where the survey was conducted in 1994). A total of 74,397 subjects (84%), 35,307 men and 39,090 women, returned their questionnaires. Frequency and daily amounts of consumption were ascertained for beverages including green tea using precoded answers (almost none; 1–2 or 3–4 days per week; 1–2, 3–4, or 5 or more cups per day for those who consume 'almost daily'). 'Almost daily' category included those who consume 5–7 days per week.

Although the style of the questions differed slightly between the two cohorts, questions concerning current or former smoking status, age at initiation of smoking, number of cigarettes consumed per day for smokers, and age at cessation of smoking for past smokers were included in both questionnaires.

Dietary factors included in the questionnaire have been reported elsewhere [17]. Briefly, the weekly intake frequency of 27 food items in four categories was reported in Cohort I and intake of 33 food items in five categories was reported in Cohort II. Food items were also slightly different between Cohort I and Cohort II, and thus for multiple adjustment of these variables, we were not able to simply combine the data sets. The statistical methods used are described below.

The family history of gastric cancer was regarded positive if one of the subject's parents or siblings had gastric cancer.

We excluded subjects with a self-reported cancer at baseline, subjects who were not Japanese, and subjects who had already moved away at the baseline, which we confirmed during the follow-up period. These exclusions left 34,832 eligible men and 38,111 women in the study.

Follow-up and identification of gastric cancer

Death and move out. Subjects were followed from January 1, 1990, to December 31, 2001, for Cohort I and from January 1, 1993 (1994 for Tomobe Town), to December 31, 1999, for Cohort II. In Japan, all death certificates are submitted to a local government office

and forwarded to the PHC in the area of residence. Mortality data are then sent to the Ministry of Health, Labour and Welfare and coded for the National Vital Statistics. The registration of deaths in Japan is required by the Family Registration Law and is believed to be complete. Therefore, all deaths of cohort subjects were based on death certificates from each PHC, whenever the subjects stayed in their original area. Any changes in residency status were identified annually through the residential registry in each area. Among study subjects, 3448 (4.7 %) moved out, 3402 (4.7 %) died, and 53 (0.07 %) were lost to follow-up within the study period.

Cancer registry for JPHC Study. Newly diagnosed cases of cancer were collected through two data sources, one from local major hospitals and the other from population-based registries (usually prefecture-wide). Candidate patients were linked by name, address, and date of birth, and entered in the cancer registry for the JPHC Study when the birth date and residence fulfilled cohort inclusion criteria. The death certificate was used as a supplementary information source for the cancer registry, by which 550 cancers were identified. Of all 6308 entries in the cancer registry as of July 2002 that were diagnosed from 1990 to 2001, 156 of those cases were not confirmed by medical records, and they accounted for 2.5% (death certificate only; DCO) of all entries in the cancer registry.

Identification of gastric cancer. Cases of gastric cancer were extracted from the cancer registry for the JPHC Study, based on site (International Classification of Diseases for Oncology [ICD-O] code: C160–169) [18]. A total of 892 cases of gastric cancer, 665 men and 227 women, were documented with a histologically proven diagnosis at surgery or autopsy (561; 63%), biopsy (294; 33%), or cytology (15; 2%), made from 1990 to 2001 for Cohort I and from 1993 to 1999 for Cohort II, as of July 2002. The diagnosis in 35 cases was based on clinical findings or unspecified evidence and was not regarded as gastric cancer cases. No DCO cases were included because the cases were restricted to subjects with a histological diagnosis.

Gastric cancers were classified into three categories; upper third, distal, and unclassified. Until quite recently in Japan, the upper-third of the stomach has been called the 'cardia', based on the guidelines for gastric cancer classification [19]. Because it seemed difficult to distinguish this from the real cardia, which is located mainly in the esophagogastric junction from the upper-third of the stomach, we combined them into one group for analysis in this study (ICD-O code C160–161). A tumor located toward the lower side of the stomach was classified as distal gastric cancer (ICD-O code C162–167). Those subsites that could not be classified because of a diffuse lesion (ICD-O code C168) or those with no information (ICD-O code C169) were categorized as an unclassified subsite. Histologic classification was based on a review of the record reported by each hospital, conducted by one of the authors [S. Sasazuki] in consultation with a pathologist. The subdivisions were made based on classification derived by Lauren [20].

Statistical analysis

A move from the study area, death of other reasons from gastric cancer, and diagnosis of gastric cancer at another subsite (for subsite analysis) were treated as censoring. Time at risk for each subject was calculated as the duration from the start of the study periods of January 1, 1990, for Cohort I and January 1, 1993, for Cohort II except for Tomobe Town (January 1, 1994) to a histological diagnosis of gastric cancer, move from the PHC area, death, or December 31, 2001, for Cohort I and December 31, 1999, for Cohort II, whichever came first. Cochran–Mantel–Haenszel statistics were used to test the baseline characteristics. Cox's proportional hazards regression model was used to estimate the relative risks (RRs) of gastric cancer according to green tea consumption. When covariates of age, PHC areas, and smoking were used in the model (RR^a in Tables 3 and 4), Cohort I and Cohort II were simply combined, because the questionnaires were essentially the same regarding smoking status for Cohort I and Cohort II, and separate analysis showed similar results. Because there was no strong evidence of heterogeneity between separate estimates when further covariates of fruit, green or yellow vegetables, salted cod roe or fish gut, rice, miso soup, black tea, and coffee were added to the model ($\chi^2 = 0.7644$, $p = 0.38$), combination of estimates of Cohort I and Cohort II data was done by weighting the separate estimates by the inverse of the estimated variance. That is, $\beta_c = (1/v_1 \times \beta_1 + 1/v_2 \times \beta_2)/(1/v_1 + 1/v_2)$, $RR_c = \exp(\beta_c)$; β_c is the combined parameter estimate, v_1 is the variance of Cohort I, β_1 is the parameter estimate of Cohort I, v_2 is the variance of Cohort II, β_2 is the parameter estimate of Cohort II, RR_c is the combined RR (RR^b in Tables 3 and 4) (Woolf's method) [21]. The weighted average procedure was also applied to the test-for-trend statistics by using $\chi^2 = (\log RR_c)^2 \times (1/v_1 + 1/v_2)$.

Age was categorized into one of six groups: 40–44, 45–49, 50–54, 55–59, 60–64, and 65–69 years, based on age at baseline. Fruit consumption was categorized into three groups: less than 2 days per week, 3–4 days per week, and almost daily. The consumption of green or yellow vegetables was the sum of the frequencies of

intake of green vegetables and yellow vegetables, and was classified into three groups: less than 4 times per week, 5–7 times per week, and more than 8 times per week. Salted cod roe or fish gut consumption was expressed as the sum of the frequencies of intake of each and was categorized into three groups: none, 1–2 times per week, and 3 or more times per week. Rice consumption was categorized in two groups: up to 3 bowls, or more than 3 bowls per day. Miso soup consumption was categorized into three groups: rare to 3–4 days per week, 1–2, and 3 or more bowls per day for those who consume almost every day. Black tea consumption was categorized into three categories: rare, 1–2, and more than 3 days per week. Coffee consumption was categorized into four groups: rare, 1–2, 3–4 days per week, and almost daily. Smoking was categorized into four groups: never, past, current smoking of 20 or less cigarettes per day, and current smoking of more than 20 cigarettes per day.

The trend was assessed by assigning ordinal values for categorical variables. Reported p values were two-sided, and all statistical analyses were done using the Statistical Analysis System (SAS) [22].

Results

Among 665 gastric cancer cases in men, 88 (13%) were upper-third gastric cancers, and 461 (69%) were distal cancers. For 227 cases in women, the corresponding numbers were 21 (9.3%) and 170 (75%), respectively. As for histological categorization, differentiated and undifferentiated types were 386 (58%) and 197 (30%), respectively, among men and 85 (37%) and 115 (51%) among women. The results for analysis based on histologic type did not differ materially, and we present the results combining these types.

Baseline characteristics of men and women according to green tea consumption are shown for Cohort I and Cohort II separately (Tables 1 and 2). For Cohort I, all listed variables were differently distributed according to green tea consumption, except for current smoking and heavy alcohol drinking in women. For Cohort II, only heavy smoking in women was not differently distributed according to green tea intake. RRs and 95% confidence intervals (CIs) of gastric cancer by subsite in relation to green tea consumption among men are shown in Table 3. Green tea consumption was not related to gastric cancer at any site.

Table 1. Baseline characteristics according to green tea consumption in men and women: Cohort I

	Men				p for Trend[a]	Women				p for Trend[a]
	Green tea consumption (cups per day)					Green tea consumption (cups per day)				
	<1	1–2	3–4	5+		<1	1–2	3–4	5+	
No.	4379	3183	3624	3942		5305	3247	3825	4130	
Age	48.8 (0.1)	48.7 (0.1)	49.6 (0.1)	51.2 (0.1)	<0.0001	49.2 (0.1)	49.0 (0.1)	48.9 (0.1)	51.0 (0.1)	<0.0001
Current smoker (%)	54.4	54.4	55.2	58.5	0.0002	5.2	5.0	3.9	6.0	0.48
Heavy smoker (%)[b]	16.4	15.6	17.0	21.8	<0.0001	0.3	0.4	0.2	0.5	0.26
Heavy smoker (%)[c]	28.1	28.7	32.0	42.4	<0.0001	0.3	0.4	0.3	0.8	0.005
Alcohol drinking, 1+ per week (%)	70.6	75.1	75.8	73.0	0.006	11.5	12.0	13.5	14.6	<0.0001
Heavy drinking (%)[d]	38.3	42.2	42.7	40.8	0.01	1.6	0.9	0.8	1.5	0.38
Fruit, daily (%)	24.9	28.5	29.2	35.0	<0.0001	47.8	53.8	54.5	57.0	<0.0001
Green or yellow vegetables, daily (%)	25.4	29.3	30.1	34.8	<0.0001	37.1	43.2	45.0	49.2	<0.0001
Pickled vegetables, daily (%)	48.2	54.8	58.5	66.7	<0.0001	59.0	63.8	69.7	77.8	<0.0001
Salted or dried fish, 3+ per week (%)	33.3	36.4	38.0	41.6	<0.0001	38.2	42.7	44.2	50.1	<0.0001
Salted cod roe or fish gut, 3+ per week (%)	50.8	54.1	53.7	54.0	0.006	39.5	43.2	43.1	48.0	<0.0001
Miso soup, daily (%)	81.6	85.4	86.1	87.5	<0.0001	78.7	82.2	82.7	82.5	<0.0001
Rice, 4+ bowls per day (%)	53.8	50.2	54.7	60.8	<0.0001	24.1	19.1	17.6	21.3	<0.0001
Coffee, daily (%)	31.4	35.9	31.1	24.2	<0.0001	32.1	38.5	29.2	21.4	<0.0001
Black tea, 1+ cups per week (%)	10.6	14.9	15.6	14.4	<0.0001	12.8	18.1	20.5	17.7	<0.0001
Family history of gastric cancer (%)	7.0	8.0	8.2	10.7	<0.0001	6.8	7.4	9.3	11.2	<0.0001
Body mass index	23.4 (0.04)	23.4 (0.05)	23.3 (0.04)	23.1 (0.04)	<0.0001	23.4 (0.04)	23.3 (0.05)	23.3 (0.05)	23.5 (0.05)	0.07

Values are means (SE) unless otherwise specified.
[a] Based on Cochran–Mantel–Haenszel statistics.
[b] Current smoker with 21+ cigarettes / day.
[c] Ever smoker with 30+ pack years.
[d] Alcohol drinking of 250+ mg ethanol per week.

Table 2. Baseline characteristics according to green tea consumption in men and women: Cohort II

	Men				*p* for Trend[a]	Women				*p* for Trend[a]
	Green tea consumption (cups per day)					Green tea consumption (cups/d)				
	<1	1–2	3–4	5+		<1	1–2	3–4	5+	
No.	2763	5028	6316	5293		2489	4477	7462	6810	
Age	51.4 (0.2)	52.0 (0.1)	53.8 (0.1)	55.9 (0.1)	<0.0001	52.4 (0.1)	52.9 (0.1)	54.6 (0.1)	56.1 (0.1)	<0.0001
Current smoker (%)	56.5	55.9	53.4	55.0	0.06	9.4	6.5	5.2	6.7	0.0001
Heavy smoker (%)[b]	20.3	20.0	18.2	20.7	0.95	0.9	0.4	0.4	0.7	0.97
Heavy smoker (%)[c]	38.7	38.6	42.9	51.1	<0.0001	1.5	0.7	0.7	1.2	0.88
Alcohol drinking, 1+ per week (%)	63.1	67.5	65.1	58.8	<0.0001	14.0	12.7	10.5	10.3	<0.0001
Heavy drinking (%)[d]	31.1	32.6	31.4	29.0	0.004	2.0	1.1	1.0	1.0	0.0005
Fruit, daily (%)	31.2	37.4	43.7	48.5	<0.0001	56.1	63.5	69.2	70.7	<0.0001
Green or yellow vegetables, daily (%)	41.7	45.8	53.9	58.6	<0.0001	59.7	63.7	70.1	71.8	<0.0001
Pickled vegetables, daily (%)	32.7	40.5	47.5	52.5	<0.0001	39.2	45.0	51.5	57.8	<0.0001
Salted or dried fish, 3+ per week (%)	40.8	45.2	49.5	50.8	<0.0001	42.0	47.1	50.6	52.8	<0.0001
Salted cod roe or fish gut, 3+ per week (%)	14.2	13.7	15.0	17.7	<0.0001	9.7	10.3	9.8	12.9	<0.0001
Miso soup, daily (%)	58.6	69.5	74.0	79.4	<0.0001	57.9	64.2	68.7	71.2	<0.0001
Rice, 4+ bowls per day (%)	32.3	32.2	37.4	41.8	<0.0001	12.1	10.9	11.5	12.7	0.06
Coffee, daily (%)	43.6	45.3	39.2	29.3	<0.0001	41.3	44.6	35.8	24.2	<0.0001
Black tea, 1+ cups per week (%)	14.0	16.4	16.4	16.7	0.008	19.1	22.3	23.4	22.4	0.005
Family history of gastric cancer (%)	5.1	5.8	6.7	6.4	0.007	5.6	5.8	6.7	6.6	0.03
Body mass index	23.4 (0.05)	23.3 (0.04)	23.1 (0.04)	23.2 (0.04)	<0.0001	23.4 (0.07)	23.3 (0.05)	23.3 (0.04)	23.5 (0.04)	0.05

Values are means (SE) unless otherwise specified.
[a] Based on Cochran–Mantel–Haenszel statistics.
[b] Current smoker with 21+ cigarettes per day.
[c] Ever smoker with 30+ pack years.
[d] Alcohol drinking of 250+ mg ethanol per week.

Table 3. RRs and 95% CIs of gastric cancer by anatomical subsite in relation to green tea consumption among men

	Green tea consumption (cups per day)				
	<1	1–2	3–4	5+	*p* for trend
All site					
RR[a] (95% CI), n = 661	1.0	0.95 (0.74–1.21)	0.89 (0.71–1.13)	0.97 (0.77–1.22)	0.81
RR[b] (95% CI), n = 610	1.0	0.94 (0.72–1.22)	0.84 (0.65–1.08)	0.98 (0.77–1.25)	0.65
Upper-third including cardia					
RR[a] (95% CI), n = 88	1.0	1.07 (0.53–2.17)	0.88 (0.44–1.75)	1.24 (0.65–2.35)	0.54
RR[b] (95% CI), n = 80	1.0	1.06 (0.51–2.18)	0.73 (0.34–1.57)	1.17 (0.60–2.30)	0.75
Distal					
RR[a] (95% CI), n = 457	1.0	0.88 (0.65–1.17)	0.85 (0.64–1.12)	0.88 (0.67–1.16)	0.42
RR[b] (95% CI), n = 423	1.0	0.88 (0.64–1.20)	0.79 (0.59–1.07)	0.92 (0.69–1.22)	0.37

[a] Calculated from a proportional hazards regression analyzing the two cohorts together. Adjusted for age, area, and cigarette smoking.
[b] Calculated from weighted average of the results from separate proportional hazards regressions fitted to the individual cohorts. Further adjusted for consumption of fruit, green or yellow vegetables, fishgut, miso soup, rice, black tea, and coffee.

When potential confounding factors were further adjusted based on the method described in the previous section, the overall results did not differ materially.

For women, a decreased risk of gastric cancer in relation to green tea consumption was observed after controlling potential confounding factors; adjusted RRs and 95% CI for 1–2, 3–4, and 5 or more cups per day compared to less than one cup per day were 0.85 (0.53–1.38), 1.04 (0.68–1.58), and 0.67 (0.43–1.04), respectively (p for trend = 0.08) (Table 4). This association was more remarkable when cancer was restricted to the distal portion; RR = 0.51 (95% CI 0.30–0.86) in the highest category (five cups or more) of green tea consumption (p for trend = 0.01).

Table 4. RRs and 95% CIs of gastric cancer by anatomical subsite in relation to green tea consumption among women

	Green tea consumption (cups per day)				
	<1	1–2	3–4	5+	*p* for trend
All site					
RR[a] (95% CI), n = 225	1.0	0.93 (0.61–1.41)	1.10 (0.75–1.60)	0.70 (0.47–1.05)	0.15
RR[b] (95% CI), n = 203	1.0	0.85 (0.53–1.38)	1.04 (0.68–1.58)	0.67 (0.43–1.04)	0.08
Upper-third including cardia					
RR[a] (95% CI), n = 21	1.0	2.28 (0.56–9.33)	0.70 (0.13–3.62)	1.74 (0.44–6.86)	0.73
RR[b] (95% CI), n = 19	1.0		0.89 (0.34–2.33)		0.81
Distal					
RR[a] (95% CI), n = 169	1.0	0.92 (0.58–1.47)	1.05 (0.69–1.60)	0.53 (0.33–0.85)	0.01
RR[b] (95% CI), n = 154	1.0	0.88 (0.52–1.49)	1.00 (0.63–1.59)	0.51 (0.30–0.86)	0.01

[a] Calculated from a proportional hazards regression analyzing the two cohorts together. Adjusted for age, area, and cigarette smoking.
[b] Calculated from weighted average of the results from separate proportional hazards regressions fitted to the individual cohorts. Further adjusted for consumption of fruit, green or yellow vegetables, fishgut, miso soup, rice, black tea, and coffee.

Discussion

In the present study, a reduced risk of gastric cancer in relation to green tea consumption was observed among women. This relationship was more notable when the tumor was localized to the distal stomach. Several explanations may be possible regarding the null association for men: the highest category included more subjects with higher consumption of green tea in women compared to men; the protective effect may be truly confined to women; the observed association in women was a mere chance finding; and the assessment of tea consumption may have been less accurate in men than in women. We have determined that the validity of green tea consumption assessed with a dietary record for 28 days is slightly lower in men compared to women, both in Cohort I and Cohort II; Spearman correlation coefficient 0.57 for men and 0.63 for women in Cohort I [22] and 0.37 for men and 0.43 for women in Cohort II (unpublished data). Another explanation is that it may be due in part to residual confounding effects, especially for cigarette smoking, in men. In our previous analysis [23], we observed a nearly twofold statistically significant increased risk of gastric cancer in relation to cigarette smoking in men. This point may also be applied to the previous cohort studies, in which potential confounding factors such as consumption of vegetables and fruits as well as cigarette smoking may not have been sufficiently controlled for. Even in these prospective studies, although not statistically significant, lower risk estimates of gastric cancer were observed among women compared to men. Tsubono *et al.* showed that adjusted RRs of gastric cancer risk for green tea consumption of 1–2, 3–4, and 5 or more cups per day were 0.8 (95% CI 0.5–1.5), 0.7 (0.4–1.3), and 0.8 (0.5–1.3), respectively, as compared with consumption of one cup per day or less in women while the corresponding values were 1.3 (0.8–1.9), 1.2 (0.8–1.8), and 1.5 (1.0–2.1) in men [6]. Furthermore, another recent study from Japan revealed that adjusted RRs of gastric cancer death for green tea consumption of 5–9, and 10 or more cups per day were 0.8 (95% CI 0.4–1.6) and 0.7 (0.3–2.0), respectively, in women. For men, the corresponding values were 1.1 (0.6–1.9) and 1.0 (0.5–2.0) [8].

Upper-third gastric cancer had no association with green tea consumption. This was observed both in men and women. Few studies have investigated the relationship between green tea consumption and gastric cancer risk considering anatomical subsite, all of which were case-control studies [24, 25]. While Ji *et al.* [25] showed no difference in risk estimates by subsite (cardia versus distal), Yu *et al.* [24] showed a different risk pattern by tumor subsite; the effect estimate for tea drinkers compared to nondrinkers was near null for the cardia site (OR = 0.95, 95% CI = 0.51–1.77) and was more notable for the pyloric site (OR = 0.29, 95% CI = 0.13–0.68) and antrum site (OR = 0.67, 95% CI = 0.41–1.08). The inconsistencies among studies may be due to some extent to different levels of misclassification of cardia cancers, such as the recent introduction of a separate diagnostic code, the lack of consensus for a definition of cardia, and an increased interest in cardia cancer [10, 26]. Yu *et al.* [24] also showed that boiling hot tea had a nonsignificant increased risk of gastric cancer (OR = 1.18, 95% CI = 0.75–1.86). The risk estimates for the cardia, pylori, and antrum sites regarding boiling hot tea were 2.09, 0.56, and 0.82, respectively. This suggests that the hot temperature of tea may be harmful rather than beneficial especially for the most proximal part of the stomach. In fact, a number of studies have found that hot drinks have an effect on esophageal cancer risk [27].

From a large prospective cohort study in Japan, Kinjo *et al.* showed that mortality risks of esophageal cancer was substantially associated with thermal effect of hot tea as well as alcohol drinking, smoking, and lower consumption of green–yellow vegetables [28]. It also has been shown that mate drinking and the habits of drinking 'burning hot' beverages were associated with esophagitis [29, 30]. It is not easy to distinguish the effect of the constituents in tea and the temperature at which the tea is consumed and further studies on this question is needed.

For women, a reduced risk of gastric cancer was observed even at an amount of 5 or more cups per day, which contradict previous findings in which reduced risk of gastric cancer was only observed at an intense dose such as 10 or more [31] or 7 or more cups per day [32]. In these studies, gender was not separately analyzed and information regarding anatomical subsite was also missing. It is possible that when these details are adequately considered, an amount of 5 cups or more per day may be sufficient to reduce the risk of gastric cancer.

A majority of previous case-control studies have shown a reduced risk of gastric cancer in relation to green tea consumption [24, 25, 32–36]. In both *in vitro* and animal studies, polyphenols isolated from green tea have also been shown to have antioxidant activities and the ability to inhibit nitrosation [2–4]. N-Nitroso compounds have been implicated as etiologic factors of gastric cancer and the protective effect of green tea may be due to its ability to inhibit the endogeneous formation of these nitroso compounds. Recent prospective studies however, contradict these findings [6–8]. Although it is true that case-control studies are susceptible to recall bias and the results must be interpreted cautiously, the quality of most of the case-control studies was reasonably high. They contained a sufficient number of cases, and some had population-based controls [24, 25, 31, 34, 35], appropriate adjustment including dietary factors specific for gastric cancer [31, 32, 34], and considered the anatomical subsite [24, 25]. Thus it does not seem that their findings are much less meaningful.

Green tea consumption was measured rather crudely; neither the size of a usual cup nor the strength of the tea brew was ascertained. Inaccurate measurement of green tea consumption necessarily results in random misclassification, which in turn attenuates the true association. However, such misclassification may not be so substantial as to produce a spurious positive or inverse association.

In recent years, accumulating data shows that *Helicobacter pylori* infection is closely associated with an increased risk of gastric cancer [36, 37]. Prevalence of *Helicobacter pylori* IgG antibody among randomly selected men aged 40–49 years were 76% in Ninohe (n = 131), 86% in Yokote (n = 133), and 72% in Saku (n = 118) PHC areas in our previous study in 1989–1990 [37], and its effect may not be negligible. The effect of *Helicobacter pylori* infection on the association between green tea consumption and gastric cancer risk, either as a confounding factor or interaction, may be clarified in future nested case-control studies.

We observed a statistically significant reduced risk of distal gastric cancer in women in a population-based cohort study. More prospective studies with detailed information are needed to confirm the role of green tea on the risk of gastric cancer.

Acknowledgments

The authors thank all staff members in each study area for their painstaking efforts to conduct the baseline survey and follow-up. The authors also thank the Iwate, Aomori, Ibaraki, Niigata, Osaka, Kochi, Nagasaki, and Okinawa cancer registries for providing incidence data. The authors are grateful to Dr S. Watanabe and Dr M. Konishi, who contributed to the initiation of the JPHC Study, and to Ms Y. Iwatare, Ms M. Takahashi, Ms M. Hosokawa, Ms F. Furuya, Ms M. Iizuka, and Ms A. Yamada for their technical assistance.

Notes

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