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Impact of body mass index on the risk of total cancer incidence and mortality among middle-aged Japanese: data from a large-scale population-based cohort study – The JPHC Study*

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Abstract

Objectives: To determine whether low or high extremes of body mass index (BMI) in otherwise healthy individuals affect mortality only after they develop cancer or affect the likelihood that cancer will occur.
Methods: We conducted a cohort analysis on the possible association between BMI and the risk of total cancer incidence and mortality among a middle-aged Japanese population consisting of a population-based cohort of 88,927 subjects (42,093 men and 46,834 women) with a 10-year follow-up.
Results: In men, a U-shaped association between BMI and cancer occurrence was observed, with men with a BMI of 23.0–24.9 having the lowest risk of cancer occurrence (BMI 14.0–18.9: HR = 1.29, 95% CI = 1.08–1.54; BMI 30.0–39.9: HR = 1.22, 95% CI = 0.92–1.61). This tendency did not change substantially after excluding cases diagnosed early during the follow-up period; cancer mortality showed a similar trend but with higher risk values. When analyzed according to smoking category, a low BMI affected cancer occurrence more strongly among current smokers than in never-smokers. Unlike men, no marked fluctuation in risk was observed in women.
Conclusions: A very low BMI seems to have an impact on the total cancer risk in populations with a low average BMI. Therefore, while much attention has been given to the effects of obesity, the health effects of both extreme ends of BMI should be taken into consideration in populations with a low average BMI.

Introduction

A high body mass index (BMI) is thought to be associated with various health conditions such as cardiovascular disease, hypertension and type II diabetes mellitus, the biological mechanisms of which have been well documented [1]. This topic has received increasing public health attention in populations where the Westernization of diet and other lifestyle factors has been underway for decades.

BMI has also been linked to cancer. According to recent expert consultation reports by World Health Organization (WHO)/Food and Agriculture Organization (FAO), a high BMI and obesity have been categorized as "convincing" risk factors for cancer of various sites, including the esophagus, colorectum, breast in postmenopausal women, endometrium and kidney [2]. The impact of BMI on total cancer has been investigated, mainly in Western developed countries [3–7]. Most of these reports have targeted cancer mortality, and they consistently observed a positive link between cancer mortality and obesity [3–6]. However, the proportion of subjects with a low BMI in most Western

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populations is generally considered to be too low to evaluate the association between a low BMI and targeted outcome [8, 9]. A limited number of studies on Asian populations, however, have not necessarily observed the same results as those observed in Western populations; in the Asian populations, an absence of risk [10] or an increased risk of total cancer mortality for both under and overweight individuals were found [11, 12]. In such populations, the proportion of obese subjects is generally low, compared with that of lean subjects. Thus, the concept of an "optimal" BMI should be reconsidered.

We were interested in whether this U-shaped effect of very low and very high BMIs on cancer mortality also affected the total cancer incidence. So far, this issue has not been previously investigated. Determining whether BMI in healthy individuals affects mortality only after they have developed cancer or similarly affects the likelihood of cancer occurrence is significant not only from an etiological point of view, but also for formulating public health policies for targeted populations. Therefore, to clarify the impact of the two extreme BMIs on the occurrence of total cancers in a middle-aged Japanese population, we conducted a cohort analysis using a large-scale population-based prospective study with a 10-year follow-up period.

Methods

Study population

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 was comprised of 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 was comprised of six PHC areas: Mito (Ibaraki Prefecture), Kashiwazaki (Nigata Prefecture), Chuohigashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture) and Suita (Osaka Prefecture). The details of the study design have been described elsewhere [12]. The study protocol was approved by the institutional review board of the National Cancer Center, Japan. In the present analysis, the Katsushika and Suita PHC areas were excluded since different definitions of the study population were applied in these areas.

The study population was defined as all registered Japanese inhabitants in the 9 PHC areas, aged 40–59 years in Cohort I and 40–69 years in Cohort II at the beginning of each baseline survey. The Japanese inhabitants were identified by the population registries maintained by the local municipalities. Initially, 116,896 subjects were identified as the study population. During the follow-up period, 210 subjects were found to be ineligible for the study and were excluded because of non-Japanese nationality (n = 51), late reports of emigration occurring before the start of the follow-up period (n = 156), and ineligibility because of an incorrect birth date (n = 3). As a result, a population-based cohort of 116,686 subjects (57,583 men, 59,103 women) was established.

Questionnaire

A baseline self-administered questionnaire survey on various 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% [13]. Subjects with a present or past history of self-reported serious illness at baseline (cancer, cerebrovascular disease, myocardial infarction, or chronic liver disease) were excluded from further analysis (n = 5073).

BMI was calculated from the self-reported height and weight using the formula of weight (kg)/height $(m)^2$. By comparing the self-reported height and weight with available data from health check-ups (11,274 men, 21,196 women), we confirmed that the self-reported BMIs were slightly lower than the measured BMIs with Spearman correlation coefficients of 0.89 in men and 0.90 in women. Thus, the self-reported data was considered appropriate for use in the present study.

Follow-up

Subjects were followed from January 1st of each year of the baseline survey until December 31, 2001. Residence status, including survival, was confirmed annually through the residential registry kept in each municipality of the study areas; for those who moved out of the area, residence status was confirmed through the municipal office of the area to which they had moved. Resident and death registration is required in Japan by the family registration law and is believed to be complete. Inspection of the resident registry 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, and the cause of death was defined according to the International Classification of Disease, 10th Version (ICD-10) [14]. Among the study subjects, 4972 died, 5312 moved out of the study

areas, and 46 were lost to follow-up within the follow-up period.

The occurrence of cancer was identified by active patient notification from the 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 location and morphology of each case were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [15]. 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 level of information quality was considered to be satisfactory for the present study. For the present analysis, the earliest date of diagnosis was used in cases with multiple primary cancers at different times. A total of 4756 newly diagnosed cancer cases were identified as of December 31, 2001. We excluded 990 subjects for whom the height and weight data was incomplete and 99 subjects with a BMI of less than 14 or more than 40 because of possibly unreliable data. As a result, 88,927 subjects (42,093 men, 46,834 women), including 4696 incident cancer cases and 1829 cancer deaths, were used for the present analysis.

Analysis

The number of person-years in the follow-up period were counted from January 1st of the baseline survey until the following endpoints: for the analysis of total cancer incidence – the date of occurrence of any cancer, the date of emigration from the study area, the date of death, or the end of the study period (December 31, 2001), whichever came first; for the analysis of total cancer deaths, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first. For persons who were 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 all cancer deaths during the study period. Hazard ratios (HR) and their 95% confidence intervals (95% CI) were used to describe the relative risk of all sites of cancer occurrence and deaths associated with BMI categories (14.0–18.9, 19.0–20.9, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, 30.0–39.9) at baseline. The HRs were also estimated separately according to smoking status to clarify whether smoking modified the association between BMI and cancer incidence or death. The Cox proportional hazards model was employed as a control for potential confounding factors, like age at baseline (continuous), study area (9 PHC areas), smoking status (pack-years [0, 1–19, 20–29, 30–39, ≥40] for men and never, former, or current for women), weekly ethanol intake (none, occasionally, ≤149 g/week, ≥150 g/week for men, and none, occasionally, ≤99 g/week, ≥100 g/week for women), green vegetable intake (everyday, less than everyday), and leisure-time physical activity (< 1 time/month, 1–3 times/month, ≥1 time/week). These variables are either known or suspected risk factors for cancer or had been found to be associated with a risk of cancer in previously reported results [12]. Stata [16] was used to perform the statistical analyses.

Results

During the 847535.2 person-years of the follow-up period (average follow-up period: 9.5 years) for the 88,927 subjects (42,093 men and 46,834 women), a total of 4696 cases of newly diagnosed cancer (2763 men and 1933 women) and 1829 cancer deaths (1181 men and 648 women) were included in the analyses. With regard to cancer incidence, gastric cancer was the most common cancer in men (n = 749, 27.1%), followed by lung cancer (n = 392) and colon cancer (n = 363); in women, breast cancer was the most common (n = 348, 18.0%), followed by gastric cancer (n = 284), and colon cancer (n = 218). With regard to cancer deaths, lung cancer was the most common cause of death from cancer in men (n = 285, 24.1%), followed by gastric cancer (n = 227) and liver cancer (n = 108); in women, gastric cancer was the most common cause of death from cancer (n = 83, 12.8%), followed by lung cancer (n = 81), and pancreatic cancer (n = 63).

At baseline (Table 1), the overall mean BMI was 23.05 in men and 23.06 in women. In men, the proportion of current smokers increased in lower BMI groups, and subjects with the lowest and highest BMIs tended to drink less alcohol than the middle BMI categories. In women, on the other hand, an increase in the proportion of current smokers was apparent only in the lowest BMI category, while subjects in the higher BMI categories tended to drink less alcohol. Both in men and women, more frequent leisure-time physical activity was observed for higher BMI categories. However, no marked difference in green vegetable intake was observed between the BMI categories.

The HRs for the subsequent occurrence of cancer according to BMI categories are presented in contrast with the ratios for cancer mortality in Table 2 (men) and Table 3 (women). In men, a U-shaped association between BMI and cancer occurrence was found, with men with a BMI of 23.0–24.9 having the lowest risk of cancer occurrence (BMI 14.0–18.9: HR = 1.29,

Table 1. Baseline characteristics of the study subjects according to body mass index category

	Body mass index						
	14.0–18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	30.0–39.9
Men (n = 42,093)							
Number of subjects	1696	6110	10,851	11,770	6979	3765	922
Proportion (%)	4.0	14.5	25.8	28.0	16.6	8.9	2.2
Age (years) ± SD	53.5 ± 8.8	52.1 ± 8.3	51.9 ± 8.0	51.5 ± 7.7	51.1 ± 7.5	50.7 ± 7.3	50.4 ± 7.2
Smoking status (%)							
Never	17.3	18.5	21.8	26.1	28.7	30.9	31.3
Former	17.7	18.3	21.4	24.6	25.6	25.7	25.7
Current	65.0	63.2	56.8	49.3	45.7	43.4	43.0
Pack-years of smoking (%)							
0 pack-years	17.3	18.5	21.9	26.1	28.8	30.9	31.2
1–19 pack-years	18.8	19.1	18.8	19.3	18.4	16.3	15.4
20–29 pack-years	19.5	21.4	19.6	17.8	15.6	16.4	13.3
30–39 pack-years	18.8	18.6	17.4	15.3	14.6	12.2	14.8
≥40 pack-years	25.6	22.4	22.3	22.5	22.6	24.2	25.3
Alcohol drinking status (%)							
None	32.6	23.5	21.8	20.8	21.1	22.0	23.5
Occasional	6.1	8.5	8.1	9.7	10.7	12.2	15.7
≤149 g/week	21.5	21.7	23.0	23.1	22.2	21.5	17.3
≥150 g/week	39.8	46.3	47.1	46.4	46.0	44.3	43.5
Green vegetable intake (%)							
Less than everyday	76.7	75.6	76.2	75.4	75.3	76.7	76.5
Everyday	23.3	24.4	23.8	24.7	24.7	23.3	23.5
Leisure-time physical activity (%)							
< 1 time/month	73.7	69.8	66.9	64.2	64.3	64.2	64.7
1–3 times/month	11.2	13.8	15.1	16.4	15.4	16.2	13.3
≥1 time/week	15.1	16.4	18.0	19.4	20.3	19.6	22.0
Women (n = 46,834)							
Number of subjects	2468	7159	12,199	11,518	7261	4695	1534
Proportion (%)	5.3	15.3	26.1	24.6	15.5	10.0	3.3
Age (years) ± SD	52.1 ± 8.7	51.0 ± 8.2	51.6 ± 7.9	52.0 ± 7.8	52.9 ± 7.7	53.3 ± 7.7	53.1 ± 7.7
Smoking status (%)							
Never	88.4	91.7	93.2	94.2	93.2	92.9	90.1
Former	1.4	1.2	1.1	1.2	1.6	1.5	2.0
Current	10.2	7.1	5.7	4.6	5.2	5.6	7.9
Alcohol drinking status (%)							
None	79.7	77.6	77.6	79.5	80.3	82.6	83.6
Occasional	8.5	10.0	10.4	10.0	10.0	8.7	9.0
≤99 g/week	7.1	8.3	8.3	7.4	6.7	5.4	4.5
≥100 g/week	4.7	4.1	3.7	3.1	3.0	3.3	2.9
Green vegetable intake (%)							
Less than everyday	69.9	68.9	68.2	68.5	68.6	69.8	68.9
Everyday	30.1	31.1	31.8	31.5	31.4	30.2	31.2
Leisure-time physical activity (%)							
< 1 time/month	81.3	77.5	75.7	74.6	75.1	76.0	76.7
1–3 times/month	5.4	7.0	7.4	7.5	6.6	6.2	6.7
≥1 time/week	13.3	15.5	16.9	17.9	18.3	17.8	16.6

95% CI = 1.08–1.54; BMI 19.0–20.9: HR = 1.14, 95% CI = 1.01–1.28; BMI 30.0–39.9: HR = 1.22, 95% CI = 0.92–1.61). This trend did not change even when cases where the cancers occurred within the first three years of the study were excluded. For total cancer mortality, a similar trend was observed, but the lower BMI categories had higher risk values (BMI 14.0–18.9: HR = 1.96, 95% CI = 1.54–2.49; BMI 19.0–20.9: HR = 1.36, 95% CI = 1.14–1.64; BMI 30.0–39.9: HR = 1.26, 95% CI = 0.81–1.94). The trend was not substantially different when cases where deaths from cancer occurred within the first three years of the follow-up period were excluded. Unlike men, no marked fluctuation in risk was observed in women except for an increased risk of total cancer mortality in the lowest BMI category.

Table 2. Hazard ratios[a] of cancer incidence and deaths according to body mass index in men (n = 42,093)

Proportion (%)	Body mass index						
	14.0–18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	30.0–39.9
	4.0	14.5	25.8	28.0	16.6	8.9	2.2
Cancer incidence							
Person-years of follow-up	15068.2	56974.5	101761.4	111194.0	66050.2	35470.7	8431.8
Total cancer incidence (n = 2763)							
Number of cases	157	466	766	725	397	197	55
Hazard ratio	**1.29**	**1.14**	1.08	1.00	0.99	1.02	1.22
(95% Confidence interval)	**(1.08–1.54)**	**(1.01–1.28)**	(0.97–1.19)	(Reference)	(0.87–1.12)	(0.87–1.20)	(0.92–1.61)
Excluding first 3 years of follow-up (n = 2105)							
Number of cases	113	360	573	550	313	155	41
Hazard ratio	**1.26**	**1.15**	1.04	1.00	1.01	1.06	1.22
(95% CI)	**(1.02–1.55)**	**(1.00–1.32)**	(0.92–1.17)	(Reference)	(0.88–1.17)	(0.88–1.27)	(0.88–1.69)
Cancer deaths							
Person-years of follow-up	15419.4	58176.9	104017.7	113433.9	67232.4	36050.0	8590.3
Total cancer deaths (n = 1181)							
Number of deaths	96	218	331	282	145	85	24
Hazard ratio	**1.96**	**1.36**	1.18	1.00	0.94	1.11	1.26
(95% CI)	**(1.54–2.49)**	**(1.14–1.64)**	(0.99–1.39)	(Reference)	(0.77–1.15)	(0.87–1.42)	(0.81–1.94)
Excluding first 3 years of follow-up (n = 1007)							
Number of deaths	74	184	282	238	129	79	21
Hazard ratio	**1.86**	**1.36**	1.18	1.00	0.98	1.22	1.36
(95% CI)	**(1.42–2.43)**	**(1.12–1.66)**	(0.99–1.41)	(Reference)	(0.79–1.22)	(0.94–1.58)	(0.86–2.15)

[a] Adjusted for years of age at baseline (continuous), study area (9 PHC areas), pack-years of smoking (0, 1–19, 20–29, 30–39, ≥40), weekly ethanol intake (none, occasionally, ≤149 g, ≥150 g), green vegetable intake (everyday, less than everyday), and leisure-time physical activity (< 1 time/month, 1–3 times/month, ≥1 time/week).

Table 3. Hazard ratios[a] of cancer incidence and deaths according to body mass index in women (n = 46,834)

Proportion (%)	Body mass index						
	14.0–18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	30.0–39.9
	5.3	15.3	26.1	24.6	15.5	10.0	3.3
Cancer incidence							
Person-years of follow-up	22990.0	68547.4	117588.5	112233.1	70629.0	45656.6	14952.1
Total cancer incidence (n = 1933)							
Number of cases	104	264	497	476	328	204	60
Hazard ratio	1.01	0.91	0.99	1.00	1.04	1.01	0.87
(95% Confidence interval)	(0.81–1.26)	(0.78–1.06)	(0.88–1.13)	(Reference)	(0.90–1.21)	(0.85–1.19)	(0.66–1.15)
Excluding first 3 years of follow-up (n = 1409)							
Number of cases	69	187	348	354	246	158	47
Hazard ratio	0.93	0.86	0.92	1.00	1.05	1.05	0.90
(95% CI)	(0.71–1.21)	(0.71–1.03)	(0.79–1.07)	(Reference)	(0.89–1.24)	(0.88–1.27)	(0.66–1.24)
Cancer deaths							
Person-years of follow-up	23308.4	69532.4	119507.1	113942.3	71812.3	46366.2	15149.0
Total cancer deaths (n = 648)							
Number of deaths	51	85	146	158	115	73	20
Hazard ratio	**1.43**	0.88	0.90	1.00	1.09	1.03	0.85
(95% CI)	**(1.03–1.95)**	(0.67–1.15)	(0.71–1.13)	(Reference)	(0.85–1.39)	(0.78–1.36)	(0.53–1.37)
Excluding first 3 years of follow-up (n = 550)							
Number of deaths	42	68	119	138	102	64	17
Hazard ratio	1.38	0.81	0.83	1.00	1.10	1.05	0.82
(95% CI)	(0.96–1.97)	(0.60–1.09)	(0.65–1.07)	(Reference)	(0.85–1.43)	(0.77–1.41)	(0.49–1.38)

[a] Adjusted for years of age at baseline (continuous), study area (9 PHC areas), smoking status (never, former, current), weekly ethanol intake (none, occasionally, ≤99 g, ≥100 g), green vegetable intake (everyday, less than everyday), and leisure-time physical activity (< 1 time/month, 1–3 times/month, ≥1 time/week).

The HRs of subsequent occurrence and death from cancer were also estimated separately with regard to smoking status at baseline for each BMI category. In men (Table 4), although both never- and current smokers retained the U-shaped tendency for increased HRs, current smokers exhibited a more prominent increase, especially in the lowest BMI category (never-smokers: HR = 1.21, 95% CI = 0.73–1.98; current smokers: HR = 1.43, 95% CI = 1.15–1.77); in the highest BMI category, a higher HR was observed for never-smokers than for current smokers (never-smokers: HR = 1.54, 95% CI = 0.88–2.68; current smokers: HR = 1.26, 95% CI = 0.83–1.91). In contrast, an elevated risk of total cancer mortality was observed for the lowest BMI categories among both never- and current smokers (never-smokers: HR = 2.32, 95% CI = 1.18–4.54; current smokers: HR = 1.87, 95% CI = 1.39–2.53). In women (Table 5), an increased risk tendency was found in the lowest BMI category among current smokers (HR = 1.63, 95% CI = 0.90–2.96), and a rather reduced risk tendency was observed in the highest BMI category (HR = 0.32, 95% CI = 0.07–1.34). In contrast, a more prominent increased risk of total cancer mortality was observed for the lowest BMI categories among current smokers, but the difference was not statistically significant (HR = 2.23, 95% CI = 0.80–6.22). In both men and women, similar tendencies with regard to cancer incidence and mortality were observed when cases where cancers occurred or subjects died from cancer within the first three years of the follow-up period were excluded.

Discussion

Although the effect of BMI on total cancer mortality has been investigated by many studies, few reports have targeted the association between BMI and total cancer occurrence[7]. Furthermore, only a few studies on the association between BMI and cancer mortality have been performed in Asian populations, which tend to have a lower average BMI than that of Western populations [10–12].

In our large-scale population-based cohort study with a 10-year follow-up period, we observed a U-shaped

Table 4. Hazard ratios[a] of cancer incidence and deaths according to body mass index and smoking status in men (n = 42,093)

		Body mass index						
		14.0–18.9	19.0–20.9	1.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	30.0–39.9
Cancer incidence								
Total cancer incidence (n = 2763)								
Never-smoker	Hazard ratio	1.21	1.03	0.81	1.00	0.88	1.06	1.54
	(95% CI)	(0.73–1.98)	(0.75–1.41)	(0.62–1.06)	(Reference)	(0.66–1.17)	(0.76–1.48)	(0.88–2.68)
Current smoker	Hazard ratio	**1.43**	**1.17**	1.09	1.00	1.03	1.02	1.26
	(95% CI)	**(1.15–1.77)**	**(1.00–1.36)**	(0.95–1.26)	(Reference)	(0.87–1.23)	(0.81–1.30)	(0.83–1.91)
Excluding first 3 years of follow-up (n = 2105)								
Never-smoker	Hazard ratio	1.29	1.05	0.76	1.00	0.96	1.16	1.35
	(95% CI)	(0.73–2.27)	(0.73–1.51)	(0.55–1.04)	(Reference)	(0.70–1.32)	(0.80–1.68)	(0.68–2.68)
Current smoker	Hazard ratio	**1.45**	**1.25**	1.12	1.00	1.08	1.05	1.34
	(95% CI)	**(1.13–1.86)**	**(1.05–1.49)**	(0.95–1.32)	(Reference)	(0.89–1.32)	(0.80–1.37)	(0.84–2.13)
Cancer deaths								
Total cancer deaths (n = 1181)								
Never-smoker	Hazard ratio	**2.32**	1.58	1.17	1.00	0.90	1.32	1.91
	(95% CI)	**(1.18–4.54)**	(0.97–2.57)	(0.76–1.80)	(Reference)	(0.55–1.49)	(0.77–2.24)	(0.81–4.52)
Current smoker	Hazard ratio	**1.87**	**1.33**	1.11	1.00	0.99	1.20	1.33
	(95% CI)	**(1.39–2.53)**	**(1.06–1.67)**	(0.90–1.38)	(Reference)	(0.75–1.30)	(0.86–1.69)	(0.72–2.46)
Excluding first 3 years of follow-up (n = 1007)								
Never-smoker	Hazard ratio	2.07	1.64	1.30	1.00	0.99	1.44	2.28
	(95% CI)	(0.95–4.50)	(0.97–2.79)	(0.82–2.05)	(Reference)	(0.58–1.69)	(0.82–2.55)	(0.95–5.46)
Current smoker	Hazard ratio	**1.88**	**1.36**	1.12	1.00	1.03	1.38	1.34
	(95% CI)	**(1.35–2.61)**	**(1.05–1.74)**	(0.88–1.42)	(Reference)	(0.77–1.39)	(0.97–1.96)	(0.68–2.65)

[a] Adjusted for years of age at baseline (continuous), study area (9 PHC areas), pack-years of smoking (≤19, 20–29, 30–39, ≥40) (current smoker only), weekly ethanol intake (none, occasionally, ≤149 g, ≥150 g), leisure-time physical activity (< 1 day/month, 1–3 days/month, ≥1 days/week) and green vegetable intake (everyday, less than everyday).

Table 5. Hazard ratios[a] of cancer incidence and deaths according to body mass index and smoking status in women (n = 46,834)

		Body mass index						
		14.0–18.9	19.0–20.9	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	30.0–39.9
Cancer incidence								
Total cancer incidence (n = 1933)								
Never-smoker	Hazard ratio	0.95	0.91	1.01	1.00	1.04	0.98	0.95
	(95% CI)	(0.75–1.21)	(0.78–1.07)	(0.89–1.15)	(Reference)	(0.89–1.21)	(0.82–1.17)	(0.71–1.26)
Current smoker	Hazard ratio	1.63	0.91	0.83	1.00	1.21	0.95	0.32
	(95% CI)	(0.90–2.96)	(0.51–1.64)	(0.48–1.43)	(Reference)	(0.69–2.13)	(0.50–1.81)	(0.07–1.34)
Cancer incidence excluding first 3 years of follow-up (n = 1409)								
Never-smoker	Hazard ratio	0.81	0.88	0.94	1.00	1.05	1.05	0.98
	(95% CI)	(0.60–1.10)	(0.73–1.07)	(0.80–1.10)	(Reference)	(0.89–1.25)	(0.86–1.28)	(0.71–1.35)
Current smoker	Hazard ratio	1.73	0.49	0.65	1.00	0.90	0.90	0.19
	(95% CI)	(0.90–3.32)	(0.22–1.06)	(0.35–1.21)	(Reference)	(0.47–1.75)	(0.44–1.83)	(0.03–1.42)
Cancer deaths								
Total cancer deaths (n = 648)								
Never-smoker	Hazard ratio	1.38	0.81	0.90	1.00	1.11	1.02	0.86
	(95% CI)	(0.97–1.97)	(0.61–1.09)	(0.71–1.14)	(Reference)	(0.87–1.43)	(0.76–1.37)	(0.52–1.43)
Current smoker	Hazard ratio	2.23	1.77	1.01	1.00	1.18	1.31	1.16
	(95% CI)	(0.80–6.22)	(0.67–4.68)	(0.37–2.74)	(Reference)	(0.39–3.53)	(0.43–3.94)	(0.24–5.67)
Cancer deaths excluding first 3 years of follow-up (n = 550)								
Never-smoker	Hazard ratio	1.30	0.80	0.85	1.00	1.13	1.02	0.87
	(95% CI)	(0.88–1.93)	(0.59–1.10)	(0.65–1.10)	(Reference)	(0.87–1.48)	(0.75–1.40)	(0.51–1.49)
Current smoker	Hazard ratio	1.95	0.84	0.64	1.00	0.97	1.33	0.58
	(95% CI)	(0.67–5.64)	(0.26–2.68)	(0.21–1.93)	(Reference)	(0.31–3.10)	(0.44–4.05)	(0.07–4.80)

[a] Adjusted for years of age at baseline (continuous), study area (9 PHC areas), weekly ethanol intake (none, occasionally, ≤99 g, ≥100 g), leisure-time physical activity (< 1 day/month, 1–3 days/month, ≥1 days/week) and green vegetable intake (everyday, less than everyday).

tendency for an increased risk of cancer occurrence according to BMI category, with a 29% increased risk in the lowest BMI categories for men. This tendency did not change substantially after cases that were diagnosed early during the follow-up period were excluded. When analyzed according to smoking category, however, a lower BMI appeared to affect the risk of cancer more strongly among current smokers than among never-smokers. In women, BMI did not appear to affect the risk of total cancer incidence or mortality. Overall, the association between BMI and cancer incidence appeared to be less conspicuous than that with cancer fatalities.

In Western middle-aged populations, the prevalence of obesity is much higher than that in Asian populations. Recent reports show that 13% of men and 19% of women are obese (BMI ≥ 30) in the European Union [17] and the 29% of men and 35% of women are obese in the United States [9]; in Japan, however, a national survey found that only 2% of men and 3% of women were obese [18]. Although the average BMI of the Japanese population has tended to increase since World War II, this trend started to level off in men and to slightly decrease in women after the 1980s [19]. The prevalence of obesity in the present study population was similar to these previously reported values and are much lower than the values reported for Western populations. We did not find any obvious signs of an increased risk of cancer incidence or mortality in the categories with a high BMI in the present study. If anything, the population-attributable fraction might be low in this population because of the low prevalence of obese subjects. On the other hand, a relatively high proportion of underweight subjects, compared with overweight ones, was observed in Japan; 19% of the men in the present study and 21% of the women had a BMI < 21, and 4% of the men and 5% of the women had a BMI < 19. In view of the relatively high proportion of lean subjects in Japan and the elevated risk of cancer incidence and mortality in the low BMI categories, the association between BMI and cancer incidence and mortality should be considered in lean populations as well as obese populations.

In the present analysis, a clear association between obesity and cancer may not have been observed because of the small proportion of cancer sites that are considered to be positively linked to bodyweight, such as esophageal adenocarcinoma and cancer of the colorectum, breast in postmenopausal women, endometrium, and kidney [1, 2]. When all the cases of breast cancer including those where the menopausal status at the time of diagnosis was not noted were included and all the rare cases of esophageal adenocarcinoma were excluded, the above cancers accounted for 22% (n = 603) of the incidence of cancer in men, and 40% (n = 776) of the incidence of cancer in women, 13% (n = 89) of the deaths from cancer in men, and 23% (n = 148) of deaths from cancer in women. These proportions were relatively high among women but not necessarily high among men, when compared to those reported in Western countries, where the incidence of these cancers were reported to be 18% in men and 48% in women in a Swedish study [7] and the percentage of deaths from these cancers was reported to be 13% in men and 28% in women in American study [6]. Therefore, our results cannot simply be explained by a difference in the distribution of cancer sites. Furthermore, additional analyses restricting the endpoints for these cancers did not show a clear positive association between an increased BMI and cancer incidence and mortality (data not shown).

An inverse association between BMI and the proportion of male current smokers was seen in our study population. Therefore, smoking status probably confounds the effects of BMI on cancer. Based on a separate analysis according to smoking status in men, lean subjects appeared to have higher risk of cancer than others, especially among smokers; a similar tendency was not observed for cancer mortality, where a similar risk was observed for both never- and current smokers. Whether the slightly elevated risk of cancer occurrence among lean male never-smokers is an actual effect of the subjects' low BMIs is difficult to assess from the present results; however, the strength of this effect, if it exists, is probably modest. Although we cannot rule out the possibility of residual confounding effects, a very low BMI status in otherwise healthy individuals may have important implications for the future occurrence of cancer.

Several mechanisms for the effects of a low or high BMI on the risk of cancer are possible. The role of obesity in cancer has been explained by endogenous hormones such as insulin, insulin-like growth factor I, sex steroids and abdominal obesity [1]. Malnutrition is also known to reduce immune responses and impair resistance to infection [20]. Over-nutrition is also thought to reduce immunity, based on animal studies [21]. Accordingly, both lean and obese subjects may have impaired immune systems, hindering the elimination of maltransformed cells before they become cancerous as well as the body's ability to fight cancer once it has become established.

The mechanism responsible for the observed differences according to gender remains unclear. No substantial effects of an extreme BMI on total cancer occurrence were observed in women. The low prevalence of current female smokers in Japanese middle-aged populations [22] may partially explain the discrepancy between the trends for the male and female populations observed in this study.

The major strength of the present study was its prospective design. Information on the subjects' BMIs were collected before subsequent diagnoses of cancer, thereby avoiding the exposure recall bias that is inherent to case-control studies. We used self-reported heights and weights to obtain the BMIs, but the correlation between these values and those from health screenings was considered to be sufficiently high to minimize BMI misclassification. Change in BMI after the start of the study arising from symptoms related to the subsequent cancer diagnosis may have resulted in some misclassification. Study subjects were selected from the general population, and the response rate of 82% to the baseline questionnaire is acceptable for 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, some geographical variation in the study area occurred. In the present study, we adjusted the study areas in the analysis to control for such geographical variations. We confirmed that the quality of the registry system was not affected by BMI status; therefore, possible misclassification of cancer occurrence by an underreporting of cancer diagnosis would be non-differential and would lead to an underestimation of the results. Since two metropolitan areas were excluded from the present analysis because they used different definitions for the study population, our results may not reflect urban Japanese populations, which is another limitation of the present study. However, the distribution of BMI was not substantially different between the metropolitan and non-metropolitan areas of the study. Therefore, the exclusion of these two metropolitan areas is unlikely to have distorted the present results.

While allowing for these methodological issues, the present analysis provides practical remarks on the impact of BMI on total cancer risk. Namely, the overall

association of BMI with cancer incidence appeared to be less conspicuous than that with cancer mortality. However, an extremely low BMI appears to have an impact on the total cancer risk in populations with a relatively low average BMI. While much attention has been given to the effects of obesity on cancer, the health effects of extremely high and low BMIs should be taken into consideration when formulating cancer prevention measures in populations with low average BMI.

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Green tea consumption and subsequent risk of gastric cancer by subsite: the JPHC Study☆

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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

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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.

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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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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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