like that combined grilled/stir-fried meat and fish intake was a better surrogate for HCA intake.

HCA intake was not calculated from 28 days DR in this study because more than 130 kinds of fish are described in the Standard Tables of Food Composition in Japan [27], and it is difficult to develop the HCA database of fish. Although a database for HCA content has recently been developed for 297 food items [11], most food items have not been analyzed in Japan. This is because meat size or thickness and cooking conditions such as cooking temperature and time in Japan are different from those in the West. These also make it difficult to calculate HCA intake in meat.

On the one hand, the PhIP level in hair of the subjects in the present study (178–3674 pg/g hair) was lower than that of a report in the USA (500–50,000 pg/g hair) [16]. However, significant relationships between the PhIP level in hair and grilled/stir-fried meat and fish intake were observed. Only the PhIP level was compared with grilled/stir-fried meat and fish intake in the present study. However, because PhIP content was correlated with other HCA content in many foods [11], the PhIP level in hair could have been a biochemical indicator of not only PhIP intake but also other HCA intake.

Intake of cruciferous vegetables has been shown to reduce the excretion of PhIP in urine, and urinary mutagenicity was elevated [28,29]. However, the effect of cruciferous vegetable consumption on the PhIP level in human hair has not been reported. Since cruciferous vegetable intake has not been estimated, we could not examine the confounding effect of this factor in the present study. The relation between the PhIP level in hair and grilled/stir-fried meat and fish intake could be attenuated by the cruciferous vegetable intake.

Hardly any subject was a great eater of the burnt fish portion in the present study. Therefore, the PhIP level in hair and intake of the burnt portion may not have been correlated. In Japan, the pan-fried method of grilled/stir-fried meat frequently refers to short cooking time and not high meat temperature. Therefore, no difference in the present study was found between the PhIP level in the hair of a person who consumed well-done grilled/stir-fried meat out of preference and those who did not. Therefore, the PhIP level in hair and frequency of well-done grilled/stir-fried meat intake may also not have been correlated.

Melanin has a demonstrated affinity for HCAs in hair and is important for the uptake of HCAs in hair [16]. In our previous report, a positive correlation was observed between PhIP levels in hair (pg/g hair) and the melanin content in hair (μg/g hair) ($r = 0.45$, 95% CI = 0.04–0.86) [17]. However, trends of the mean PhIP levels in hair within tertile of corresponding grilled/stir-fried meat and fish intake estimated from DR were found to be no different between the crude levels (pg/g hair) and the levels per melanin content (ng/g melanin). There is a possibility that other polymers such as keratin may bind PhIP [30].

In conclusion, this study has shown that the PhIP level in hair could be used as a biochemical indicator of dietary intake of HCAs. These findings enable us to assess the relative validity of dietary HCA intake estimated from FFQ in comparison with the level in human hair.

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Body mass index, body height, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based Prospective Study

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Abstract

Objective: To investigate the association of body mass index (BMI) or body height with colorectal cancer incidence in a population-based prospective study.
Methods: We identified 986 (626 men and 360 women) newly diagnosed cases of colorectal cancer during the 9.4-year follow-up of a cohort consisting of 102,949 (49,158 male and 53,791 female) middle-aged and elderly Japanese.
Results: Lower BMI groups (lower than 23) were not associated with colorectal cancer compared with the 23–24.9 BMI group. Any categories of 25–26.9, 27–29.9, or 30 or more BMI were associated with an increased risk of colorectal cancer compared with the lower than 25 BMI (RR, 1.2 for 25–26.9, 1.4 for 27–29.9, and 1.5 for 30 or more; p for trend, 0.004) in men. These associations were more evident only in invasive-type cancer analysis. BMI was not associated with the risk of colorectal cancer in women. No significant association with height was obtained for either men or women.
Conclusions: The association of BMI with colorectal cancer was confirmed in a Japanese population as well as Western populations. Only invasive-cancer analysis suggested that BMI was important for tumor growth and proliferation. Approximately 6.7% of colorectal cancer was attributable to a BMI of 25 or higher in middle-aged and elderly Japanese men.

Introduction

Colorectal cancer is one of the most common cancers in both Western and Asian populations, including Japan. Particularly, the Japanese population has shown a rapidly increasing colorectal cancer incidence for several decades [1]. Thus, analytic epidemiology to elucidate risk factors for this cancer is an important and urgent issue in order to provide evidence for its prevention.

Many epidemiologic studies have investigated an association of body mass index (BMI) with colorectal cancer and adenoma [2, 3] mostly in Western populations [4–23] but rarely in Asian populations [24–26]. Most of these studies reported a positive association and a linear trend, especially in men. Obesity causes insulin resistance and leads to a high exposure of insulin-like growth factor I (IGF-I) [27]. These hormones, insulin and IGF-I, relate to colorectal carcinogenesis in animal studies and epidemiologic studies [3, 27, 28]. In the Japanese population, weight, as well as height, has been increasing in recent decades [29]. Simultaneously, body mass index (BMI) has elevated [30]. However, the overweight population (25 or higher BMI; 24% in men and 21% in women in 1991–1995) in Japan is lower than in Western populations [29–32]. Nevertheless, the incidence rate of colorectal cancer in the Japanese population has now reached the highest level in the world [1].

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This phenomenon may be due to an increase in the number of high BMI individuals, and thus the BMI in Japan may more strongly affect colorectal carcinogenesis than in Western populations. Even 25 to 29.9 BMI subjects may be associated with a much higher risk, and this may be causing the rapid increase of colorectal cancer in the Japanese population. In addition, the risk to leaner individuals (lower than 25 BMI) should be carefully examined in Asian populations, because even the lower than 25 BMI subjects have greater disease risks such as type 2 diabetes and cardiovascular diseases than Western individuals [33].

Some studies reported that the effects of BMI differed among site-specific cancers. Distal colon cancer is more strongly associated with BMI than proximal colon cancer in many studies [5, 8, 16, 17, 19], while proximal colon is associated with a clearer risk than distal colon in a few studies [23]. This site-specific evidence, however, is too limited for a conclusive statement and should be confirmed by larger prospective studies.

Some mechanisms of BMI for colorectal cancer include the hypothesis of colonic cell proliferation by insulin and IGF-I [27, 28]. If this hypothesis is true, at least BMI would be associated with a stage of tumor growth and infiltration. In fact, some studies reported a stronger association with large rather than small adenomas [20–23, 26]. However, this evidence is insufficient, and a study on non-invasive-type and invasive-type cancer is needed.

Furthermore, body height has been another body size measure investigated for a possible association with colorectal cancer. The evidence, however, is inconsistent. Most cohort studies [4, 7, 9–11, 25] reported a positive association, but most case-control studies failed to show significant associations [15, 16, 18, 21] despite this variable with a lower recall bias. Japanese mean body height has increased in recent decades [29], and may be associated with an elevated colorectal cancer incidence.

We previously reported a high population-attributable fraction of alcohol consumption and smoking for colorectal cancer incidence in Japanese men [34]. We used here the same population of the Japan Public Health Center-based Prospective Study and investigated an association between BMI or body height and colorectal cancer incidence focusing on differences among tumor sites and the degree of invasion.

Materials and methods

Study population

The Japan Public Health Center-based Prospective Study (JPHC study) Cohort I was defined in 1990 and Cohort II in 1993 [35]. Study subjects were mainly all residents living in several municipalities in each Public Health Center area, aged 40 to 59 for Cohort I and aged 40 to 69 for Cohort II. Additionally, Cohort I included health check-up examinees and Cohort II included health check-up examinees and a random sample aged 40 to 69 from a municipality. The study subjects were identified by the population registry in each municipality. Because cancer incidence data were not available, Cohort I health check-up examinees were excluded in this report. Thus, we defined a cohort of 65,803 men (27,063 in Cohort I; 38,740 in Cohort II) and 67,520 women (27,435 in Cohort I; 40,085 in Cohort II). This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan. The study design is described in detail elsewhere [34–40].

Baseline survey

Study subjects were asked about their personal and familial medical histories, smoking, alcohol consumption, dietary habits, and other lifestyle factors by a self-administered questionnaire [36–38]. Their dietary habits were assessed by a 44-item food frequency questionnaire (FFQ) in Cohort I [41] and a 52-item FFQ in Cohort II. Altogether, 50,456 men (77%) and 55,909 women (83%) returned the questionnaire.

Assessment of exposure

Respondents reported current height (cm) and weight (kg) at baseline. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). These self-reported height and weight data were validated in our previous report [39]. We categorized BMI as follows: less than 19, 19–20.9, 21–22.9, 23–24.9, 25–26.9, 27–29.9, and 30 or more [39, 40]. Body height was divided into quintiles by sex.

Concerning potential confounding factors, we used age at baseline, alcohol consumption, smoking [34], miso (soybean paste) soup intake, and refraining from salty foods and animal fats in the BMI analysis, because these potential confounding factors were selected by a 10% change-in-estimate strategy in the highest category [42]. In body height analysis, we used age at baseline, alcohol consumption, smoking, and body weight at baseline, selected by the same strategy. Other factors such as medical history, family medical history, medication, health check-up, total energy intake, food intake frequency such as vegetables, meats, fish and rice, physical exercise, occupation, and reproductive health in women were also examined as confounding factors but not included in a final multivariate-adjusted model.

Follow-up

We followed study subjects until 31 December 2001. When subjects died, we used mortality data from the Ministry of Health, Labor and Welfare. Subjects moving to other municipalities were also annually identified through residential registers in PHC areas. Among study subjects, 9.6% moved away, and 0.2% were lost to follow-up during the study period.

Identification of colorectal cancer incidence

Up to 31 December 2001, 1064 incident cases of colorectal cancer were identified (C180–C209 in the International Classification of Diseases for Oncology, Third edition (ICD-O-3); Ref. [43]). For multiple primary cancers of the colon or rectum at different times, the earliest diagnosis was applied. For those occurring simultaneously, the most advanced and most invasive types of tumor were applied. Among these incident cases, 986 were pathologically confirmed as adenocarcinoma (626 in men and 360 in women). Such cases were further classified into two groups according to the depth of tumor invasion, i.e., invasive cancer over a mucosal layer corresponding to code 3 (Malignant, primary site) in "behavior code for neoplasms" (415 colon cases and 259 rectal cases), and non-invasive cancer within a mucosal layer corresponding to code 2 (Carcinoma *in situ*; 219 colon and 63 rectum) in ICD-O-3 (the depth in 19 colon and 11 rectal tumors were unknown). We categorized these colorectal cancer cases into site-specific cases as follows: C180–C189 for colon cancer; C180–C185 for proximal colon cancer; C186 and C187 for distal colon cancer; and C199 and 209 for rectal cancer. The proportion of cases for which information was available only from death certificates (DCO) was 1.7% for colorectal cancer and 4.1% for all cancers during the study period. These figures were considered of satisfactory quality for the present study based on the international standard [1].

Statistical analysis

We excluded ineligible subjects notified during this study period, such as non-Japanese (31 men and 20 women), those who had already moved away at baseline (107 men and 69 women), those outside the age parameters (one man and five women), and any duplication of subjects registered in our cohort (two men and one woman). From baseline questionnaire respondents, we excluded subjects with a self-reported medical history of cancer and with a diagnosis of colorectal cancer before the baseline questionnaire survey (740 men and 1503 women). Finally, we excluded subjects with incomplete body height and weight items (540 men and 597 women), leaving 49,158 men and 53,791 women as study subjects.

We calculated person-years of follow-up from the start in each cohort until the date of diagnosis of colorectal cancer, the date of a subject's death, the date of moving from a PHC area, or 31 December 2001, whichever occurred first. The mean follow-up period was 9.4 years in both cohorts together (11.3 years in Cohort I and 8.1 years in Cohort II).

Relative risks (RR) and 95% confidence intervals (CI) of colorectal cancer incidence for BMI and body height were estimated by the Cox proportional hazards model, according to the SAS PHREG procedure [44]. The estimates were adjusted for the following potentially confounding factors incorporated into the model: age (continuous), alcohol consumption (never, one to three days per month, 1–149 g/week ethanol, 150–299 g/week ethanol, 300 g/week or more ethanol), smoking (never, past, current), miso soup intake (less than 1 cup/day, 1 cup/day, 2 cups/day, 3 or more cups/day), refraining from salty foods (yes or no) and animal fats (yes or no), body weight (quintiles by sex) and PHC area. The linear trend of BMI and body height was assessed by assignment of the median value in each category. p-values for those trends were evaluated using the two-sided test with 0.05 as the significance level.

First, we estimated the RR of all cases of colorectal cancer in each cohort. These RR estimates were integrated by the fixed-effect model, as a weighted mean by the inverse of the variance. Second, after confirming no statistically significant heterogeneity across two cohorts, we combined their datasets and calculated the RRs and the linear trends for BMI. We estimated RRs of site-specific colorectal cancer. In such site-specific analyses, we considered the cancer events in the other sites as censored cases. Similarly, RRs of only invasive cancers were calculated. In such invasive-cancer analyses, non-invasive cancers were defined as censored cases.

The population-attributable fraction (PAF) was estimated by P_e $(RR_a - 1)/RR_a$, where P_e was the prevalence of exposure among incident cases and RR_a was the adjusted RR [45]. The PAFs' 95% CI were estimated by the formula of Greenland [46]. We estimated the PAFs of overweight subjects (25 or higher BMI) to normal weight subjects (lower than 25 BMI).

Results

Moderate body mass index (BMI) categories (21–22.9 and 23–24.9) applied to a large percentage of male and

Table 1. Baseline characteristics by body mass index category in men and women

	Body mass index (kg/m^2)						
	< 19	19–20.9	21–22.9	23–24.9	25–26.9	27–29.9	30+
Men in Cohort I , Number	704	2913	5226	5750	3448	1752	420
Proportion (%)	3.5	14.4	25.8	28.5	17.1	8.7	2.1
BMI (kg/m^2), median	18.3	20.2	22.0	24.0	25.8	27.9	31.2
Age (y), mean	49.9	49.5	49.6	49.3	49.2	49.3	49.5
Alcohol consumption 1 day/week or more (%)	62.3	68.8	69.9	69.9	67.5	62.6	56.5
Current smokers (%)	65.8	64.4	56.8	49.7	47.1	42.8	42.4
Miso soup intake 1 cup/day or more (%)	77.3	80.5	80.9	77.6	74.6	70.9	67.1
Refraining from salty foods (%)	66.1	66.1	72.1	74.6	76.1	76.1	75.9
Refraining from animal fats (%)	52.8	53.5	62.5	68.5	70.4	70.9	71.3
Physical exercise once or more per week (%) >	12.9	14.5	17.2	17.5	19.8	19.1	24.6
Total energy intake per day (kcal), median[a]	2033	2135	2159	2095	2020	1957	1883
Men in Cohort II, Number	1387	4312	7503	7941	4636	2550	616
Proportion (%)	4.9	14.9	26.0	27.5	15.9	8.7	2.0
BMI (kg/m^2), median	18.3	20.2	22.1	23.9	25.9	28.0	31.2
Age (y), mean	55.1	53.6	53.2	52.8	52.3	51.5	51.2
Alcohol consumption 1 day/week or more (%)	59.8	66.7	69.8	69.2	68.0	66.6	62.4
Current smokers (%)	63.7	61.3	56.0	49.0	45.0	44.9	43.2
Miso soup intake 1 cup/day or more(%)	62.7	65.9	65.9	66.2	64.0	63.6	62.1
Refraining from salty foods (%)	63.3	64.5	68.4	70.8	70.4	69.6	69.8
Refraining from animal fats (%)	56.4	61.0	65.1	68.6	69.4	69.5	71.6
Physical exercise once or more per week (%)	16.6	17.8	20.0	22.0	21.3	20.1	19.2
Total energy intake per day (kcal), median[a]	1610	1675	1672	1658	1655	1666	1688
Women in Cohort I, Number	1058	3244	5661	5427	3444	2191	700
Proportion (%)	4.9	14.9	26.1	25.0	15.8	10.1	3.2
BMI (kg/m^2), median	18.3	20.2	22.1	23.9	25.9	28.0	31.5
Age (y), mean	49.0	48.6	49.3	49.7	50.3	50.4	50.4
Alcohol consumption 1 day/week or more (%)	11.8	12.4	11.9	9.9	10.0	8.4	7.3
Current smokers (%)	10.4	7.1	5.2	4.5	4.9	5.9	8.0
Miso soup intake 1 cup/week or more (%)	77.2	75.9	75.9	74.4	74.6	72.4	67.3
Refraining from salty foods (%)	81.3	81.8	85.4	86.8	86.2	86.4	84.7
Refraining from animal fats (%)	64.6	70.8	77.5	81.2	80.8	82.9	81.4
Physical exercise once or more per week (%)	11.6	13.0	14.3	15.6	14.3	13.8	13.8
Total energy intake per day (kcal), median[a]	1370	1364	1372	1368	1361	1346	1318
Women in Cohort II, Number	2145	5572	8492	7432	4509	2907	1009
Proportion (%)	6.7	17.5	26.5	23.2	14.0	9.0	3.1
BMI (kg/m^2), median	18.3	20.2	22.0	23.9	25.9	28.0	31.6
Age (y), mean	52.7	51.4	52.7	53.7	54.8	55.3	54.8
Alcohol consumption 1 day/week or more (%)	17.5	17.8	14.8	12.8	10.6	9.7	7.8
Current smokers (%)	12.2	9.0	7.4	5.4	6.0	6.2	8.7
Miso soup intake 1 cup/day or more (%)	56.7	57.4	59.6	62.0	62.6	62.4	59.0
Refraining from salty foods (%)	81.5	83.5	84.6	85.7	85.1	86.2	85.0
Refraining from animal fats (%)	71.1	73.9	79.5	81.7	81.9	82.5	81.9
Physical exercise once or more per week (%)	17.3	19.9	20.6	20.6	21.4	20.8	17.8
Total energy intake per day (kcal), median[a]	1084	1091	1076	1071	1064	1037	1028

[a] Based on the food frequency questionnaire.

female subjects (approximately 50% in these two categories alone: Table 1). The proportion of men drinking one day per week or more was smaller in both the lowest and the highest category of BMI than in other categories. Female drinkers one day per week or more accounted for a smaller proportion in the higher BMI categories. High BMI men were less likely to have smoking habits. Higher BMI subjects tended to take less miso soup except for Cohort II women and to refrain more from salty foods and animal fats. Taller subjects had greater body weight and more energy intake, and tended to do physical exercise (Table 2).

Table 2. Baseline characteristics by body height category in both sexes

		Body height (cm)				
		Q1	Q2	Q3	Q4	Q5
Men						
	Range	< 160	160–162	163–165	166–169	170+
Cohort I	Number	4212	4029	4829	3400	3743
	Proportion (%)	20.7	19.9	24.0	16.8	18.6
	Height (cm), median	156	160	164	168	172
	Weight (kg), median	57	60	63	65	69
	BMI (kg/m^2), median	23.5	23.4	23.5	23.3	23.2
	Age (y), mean	51.7	50.2	49.4	48.3	47.3
	Alcohol consumption 1 day/week or more (%)	63.3	67.0	69.0	70.0	72.1
	Current smokers (%)	49.7	52.4	52.4	52.8	58.4
	Physical exercise once or more per week (%)	14.1	17.2	18.2	18.9	19.4
	Total energy intake per day (kcal), median[a]	2057	2045	2094	2087	2141
Cohort II	Number	5734	5364	6232	5080	6535
	Proportion (%)	19.3	18.4	21.5	17.8	22.9
	Height (cm), median	156	160	164	168	172
	Weight (kg), median	56	60	63	65	70
	BMI (kg/m^2), median	23.2	23.4	23.3	23.2	23.3
	Age (y), mean	58.1	54.7	53.1	50.9	48.7
	Alcohol consumption 1 day/week or more (%)	63.4	63.9	67.0	70.6	73.2
	Current smokers (%)	44.6	50.1	53.0	54.7	57.6
	Physical exercise once or more per week (%)	18.5	20.2	19.6	20.9	21.6
	Total energy intake per day (kcal), median[a]	1633	1635	1664	1665	1697
Women						
	Range	< 148	148–150	151–153	154–156	157+
Cohort I	Number	4200	5621	4548	3585	3771
	Proportion (%)	19.3	25.8	21.0	16.5	17.3
	Height (cm), median	145	149	152	155	159
	Weight (kg), median	50	52	54	55	58
	BMI (kg/m^2), median	23.8	23.6	23.4	23.2	22.7
	Age (y), mean	51.3	50.1	49.4	49.0	47.7
	Alcohol consumption 1 day/week or more (%)	8.0	9.3	11.3	11.8	13.5
	Current smokers (%)	5.4	4.9	5.3	6.0	7.1
	Physical exercise once or more per week (%)	12.7	12.7	14.9	15.0	16.8
	Total energy intake per day (kcal), median[a]	1338	1351	1374	1370	1389
Cohort II	Number	5696	7316	6317	5745	6992
	Proportion (%)	17.7	22.8	19.7	17.9	21.8
	Height (cm), median	145	149	152	155	159
	Weight (kg), median	49	52	53	55	57
	BMI (kg/m^2), median	23.8	23.1	23.1	22.8	22.3
	Age (y), mean	58.6	55.3	53.0	51.5	49.3
	Alcohol consumption 1 day/week or more (%)	7.1	10.7	13.7	15.5	19.8
	Current smokers (%)	4.8	6.1	7.1	8.1	9.9
	Physical exercise once or more per week (%)	18.4	19.1	20.4	20.9	22.2
	Total energy intake per day (kcal), median[a]	1043	1056	1077	1077	1096

[a] Based on the food frequency questionnaire.

The highest BMI group (30 or more) was associated with a non-significant increased risk of colorectal cancer compared with the 23–24.9 group in men of both cohorts [multivariate relative risk (RR), 1.5; 95% confidence interval (CI), 0.7–3.2 in Cohort I; RR, 1.3; 95% CI, 0.6–3.0 in Cohort II; Table 3]. Because groups of lower than 23 BMI showed almost the same risk as the 23–24.9 group, we combined these categories and repeatedly calculated RRs with a referent group of lower than 25 BMI. As a result, RR for such BMI categories had a non-significant linear trend in Cohort I (p for trend, 0.17) and a significant linear trend in Cohort II (p for trend, 0.005).

In contrast, BMI had no association with colorectal cancer in women in both cohorts (Table 3). RRs of the 30 or higher group were 0.8 (95% CI, 0.3–2.2) in Cohort I and

Table 3. Relative risks (RR) and 95% confidence intervals (CI) of colorectal cancer for body mass index by each cohort in men and women

	Body mass index (kg/m^2)							*p* for trend
	< 19	19–20.9	21–22.9	23–24.9	25–26.9	27–29.9	30+	
Men								
Cohort I (1990–2001)								
Case	13	46	80	81	58	24	10	
Person-year	7536	32122	57958	64133	38206	19395	4562	
Age-adjusted RR[a]	1.3	1.1	1.0	1.0	1.2	1.1	1.9	
95% CI	(0.7–2.3)	(0.7–1.5)	(0.8–1.4)	(reference)	(0.9–1.7)	(0.7–1.7)	(0.97–3.7)	
Multivariate RR1[b]	1.3	1.1	1.0	1.0	1.3	1.1	1.5	
95% CI	(0.7–2.4)	(0.7–1.6)	(0.7–1.4)	(reference)	(0.9–1.8)	(0.7–1.7)	(0.7–3.2)	
Multivariate RR2[b]			1.0		1.2	1.1	1.5	0.17
95% CI			(reference)		(0.9–1.7)	(0.7–1.6)	(0.7–3.0)	
Cohort II (1993–2001)								
Case	10	49	73	86	55	34	7	
Person-year	10689	34309	59693	63285	37189	20644	4861	
Age-adjusted RR[a]	0.6	0.9	0.8	1.0	1.2	1.5	1.3	
95% CI	(0.3–1.1)	(0.7–1.3)	(0.6–1.2)	(reference)	(0.8–1.6)	(0.98–2.2)	(0.6–2.9)	
Multivariate RR1[b]	0.6	1.0	0.8	1.0	1.1	1.6	1.3	
95% CI	(0.3–1.2)	(0.7–1.4)	(0.6–1.1)	(reference)	(0.8–1.6)	(1.1–2.4)	(0.6–3.1)	
Multivariate RR2[b]			1.0		1.2	1.8	1.5	0.005
95% CI			(reference)		(0.9–1.7)	(1.2–2.5)	(0.6–3.3)	
Weighted mean estimates by the inverse of variance between Cohort I and II								
Multivariate RR2[b]			1.0		1.2	1.4	1.5	
95% CI			(reference)		(0.99–1.5)	(1.1–1.9)	(0.86–2.5)	0.003
Women								
Cohort I (1990–2001)								
Case	6	21	49	38	39	18	5	
Person-year	11804	36861	64361	62514	39360	25008	8051	
Age-adjusted RR[a]	0.8	1.0	1.3	1.0	1.6	1.2	1.0	
95% CI	(0.4–2.0)	(0.6–1.7)	(0.8–1.9)	(reference)	(1.02–2.5)	(0.7–2.0)	(0.4–2.6)	
Multivariate RR1[b]	0.8	1.0	1.2	1.0	1.6	1.1	0.8	
95% CI	(0.3–2.0)	(0.6–1.7)	(0.8–1.9)	(reference)	(1.02–2.5)	(0.7–2.0)	(0.3–2.2)	
Multivariate RR2[b]			1.0		1.5	1.1	0.7	0.51
95% CI			(reference)		(1.04–2.1)	(0.7–1.8)	(0.3–2.0)	
Cohort II (1993–2001)								
Case	10	30	53	38	33	15	5	
Person-year	17051	45205	69886	61852	37717	24495	8509	
Age-adjusted RR[a]	1.0	1.3	1.3	1.0	1.3	0.9	0.9	
95% CI	(0.5–2.0)	(0.8–2.0)	(0.9–2.0)	(reference)	(0.8–2.1)	(0.5–1.6)	(0.4–2.3)	
Multivariate RR1[b]	1.0	1.4	1.4	1.0	1.3	1.0	1.0	
95% CI	(0.5–2.3)	(0.9–2.3)	(0.9–2.3)	(reference)	(0.8–2.2)	(0.5–1.9)	(0.4–2.7)	
Multivariate RR2[b]			1.0		1.1	0.8	0.8	0.56
95% CI			(reference)		(0.7–1.6)	(0.5–1.4)	(0.3–2.0)	
Weighted mean estimates by the inverse of variance between Cohort I and II								
Multivariate RR2[b]			1.0		1.3	0.9	0.8	
95% CI			(reference)		(0.98–1.7)	(0.7–1.4)	(0.4–1.5)	0.95

[a] Adjusted for age (continuous) and Public Health Center areas.

[b] Adjusted for age (continuous), Public Health Center areas, smoking (never, past current), alcohol consumption (non-drinkers, 1–3 days/month, 1–149 g/week ethanol, 150–299 g/week, 300 or more g/week), miso soup intake (less than 1 cup/day, 1 cup/day, 2 cups/day, 3 or more cups/day), refraining from salty foods and animal fats.

1.0 (95% CI, 0.4–2.7) in Cohort II, compared with the 23 to 24.9 BMI group. These estimates remained almost unchanged after stratification by age or menopausal status at baseline (data not shown).

Next, RRs of overall and site-specific colorectal cancers were calculated together with both cohorts' data, separated by sex (Table 4). Overall RRs (95% CI) of colorectal cancer in both cohorts were 1.2 (0.98–1.5) for

Table 4. Relative risks (RR) and 95% confidence intervals (CI) of site-specific colorectal cancer for body mass index in both cohorts

	Body mass index (kg/m^2)				*p* for trend
	<25	25–26.9	27–29.9	30+	
Men					
Person-years	329724	75395	40039	9423	
Colorectal cancer	438	113	58	17	
RR[a]	1.0	1.2	1.4	1.5	0.004
95% CI	(reference)	(0.98–1.5)	(1.04–1.8)	(0.9–2.5)	
Invasive colorectal cancer	285	74	44	15	
RR[a]	1.0	1.2	1.6	1.9	0.001
95% CI	(reference)	(0.9–1.6)	(1.1–2.2)	(1.05–3.4)	
Colon cancer	291	80	41	12	
RR[a]	1.0	1.3	1.5	1.4	0.003
95% CI	(reference)	(1.02–1.7)	(1.08–2.1)	(0.7–2.8)	
Invasive colon cancer	173	47	31	11	
RR[a]	1.0	1.3	1.9	2.2	<0.001
95% CI	(reference)	(0.9–1.9)	(1.3–2.8)	(1.1–4.4)	
Proximal colon cancer	110	34	17	4	
RR[a]	1.0	1.7	1.8	1.8	0.003
95% CI	(reference)	(1.1–2.5)	(1.1–3.0)	(0.7–5.0)	
Invasive proximal colon cancer	73	17	12	4	
RR[a]	1.0	1.3	1.9	2.7	0.01
95% CI	(reference)	(0.8–2.2)	(1.02–3.6)	(0.99–7.6)	
Distal colon cancer	169	44	23	8	
RR[a]	1.0	1.2	1.4	1.3	0.13
95% CI	(reference)	(0.8–1.6)	(0.9–2.1)	(0.5–3.2)	
Invasive distal colon cancer	96	29	19	7	
RR[a]	1.0	1.3	2.0	1.8	0.006
95% CI	(reference)	(0.9–2.1)	(1.2–3.3)	(0.7–5.0)	
Rectal cancer	147	33	17	5	
RR[a]	1.0	1.0	1.2	1.6	0.40
95% CI	(reference)	(0.7–1.5)	(0.7–1.9)	(0.6–3.9)	
Invasive rectal cancer	112	27	13	4	
RR[a]	1.0	1.1	1.1	1.5	0.39
95% CI	(reference)	(0.7–1.7)	(0.6–2.0)	(0.5–4.1)	
Women					
Person-years	369533	77077	49503	16560	
Colorectal cancer	245	72	33	10	
RR[a]	1.0	1.3	0.9	0.8	0.94
95% CI	(reference)	(0.97–1.7)	(0.6–1.4)	(0.4–1.5)	
Colon cancer	155	48	21	5	
RR[a]	1.0	1.3	0.9	0.5	0.73
95% CI	(reference)	(0.9–1.8)	(0.6–1.4)	(0.2–1.4)	
Proximal colon cancer	79	21	10	2	
RR[a]	1.0	1.1	0.8	0.5	0.47
95% CI	(reference)	(0.7–1.8)	(0.4–1.6)	(0.1–2.1)	
Distal colon cancer	70	26	9	3	
RR[a]	1.0	1.6	0.9	0.6	0.87
95% CI	(reference)	(0.98–2.5)	(0.4–1.8)	(0.1–2.5)	
Rectal cancer	90	24	12	5	
RR[a]	1.0	1.2	1.0	1.3	0.56
95% CI	(reference)	(0.8–2.0)	(0.5–1.8)	(0.5–3.1)	

[a] Adjusted for age (continuous), Public Health Center areas, smoking (never, past current), alcohol consumption (non-drinkers, 1–3 days/month, 1–149 g/week ethanol, 150–299 g/week, 300 or more g/week), miso soup intake (less than 1 cup/day, 1 cup/day, 2 cups/day, 3 or more cups/day), refraining from salty foods and animal fats.

the 25 to 26.9 group, 1.4 (1.04–1.8) for the 27 to 29.9 group, and 1.5 (0.9–2.5) for the 30 or higher group (*p* for trend, 0.004). We also calculated RR for an integrated category of 27 to 29.9 and 30 or higher, because the number of events in the 30 or higher group was very small. This RR was 1.4 (95% CI, 1.1–1.8).

Proximal colon cancer was strongly associated with BMI categories: 1.7 (1.1–2.5) for the 25–26.9 group; 1.8 (1.1–3.0) for the 27–29.9 group; and 1.8 (0.7–5.0) for the 30 or higher group compared with the lower than 25 group (p for trend, 0.003). RR for 27 or higher BMI was similar to the 27–29.9 or 30 or more group (RR, 1.8; 95% CI, 1.1–2.9). In women, however, no association was detected in any site-specific colorectal cancers.

In addition, invasive-type-cancer analyses showed a clearer association with BMI in men (Table 4). RRs of invasive colorectal cancer had a clearer linear trend as follows: RR, 1.2 for 25–26.9, 1.6 for 27–29.9, and 1.9 for 30 or higher [1.6 (1.2–2.2) for 27 or higher; p for trend, 0.001], compared with RRs in non-invasive and invasive analysis (1.2, 1.4, and 1.5 for respective categories in Table 4). RRs trend did not differ between proximal and distal colon cancer in this invasive-type-cancer analysis. RR for 27 or higher was also similar between proximal (RR, 2.1; 95% CI, 1.2–3.6) and distal (RR, 1.9; 95% CI, 1.2–3.1) colon cancer. The results did not change in invasive-type-cancer analyses in women (data not shown).

We estimated the population-attributable fraction (PAF) at 3.3% for the 25–26.9 group, 2.6% for the 27–29.9 group, and 0.9% for the 30 or higher group compared with the lower than 25 BMI group. As a whole, 6.7% (95% CI, 1.6–12) of colorectal cancer and 8.9% (95% CI, 2.5–15) of invasive-type colorectal

Table 5. Relative risks (RR) and 95% confidence intervals (CI) of colorectal cancer for body height by each cohort in men and women

	Body height (cm)					p for trend
	Q1	Q2	Q3	Q4	Q5	
Men						
Range	< 160	160–162	163–165	166–169	170+	
Cohort I (1990–2001)						
Case	67	71	68	61	45	
Person-year	47117	44915	53565	37417	40898	
Multivariate-adjusted RR[a]	1.0	1.2	1.0	1.4	1.0	0.74
95% CI	(reference)	(0.9–1.7)	(0.7–1.4)	(0.95–2.0)	(0.6–1.5)	
Cohort II (1993–2001)						
Case	69	60	75	46	64	
Person-year	46726	43228	49880	40013	50823	
Multivariate-adjusted RR[a]	1.0	1.1	1.2	1.0	1.3	0.37
95% CI	(reference)	(0.7–1.5)	(0.9–1.8)	(0.6–1.5)	(0.8–1.9)	
Weighted mean estimates by the inverse of variance between Cohort I and II						
Case	136	131	143	107	109	
Person-year	93843	88143	103444	77430	91720	
Multivariate-adjusted RR[a]	1.0	1.1	1.1	1.2	1.1	0.39
95% CI	(reference)	(0.9–1.5)	(0.9–1.4)	(0.9–1.6)	(0.8–1.5)	
Women						
Range	< 148	148–150	151–153	154–156	157+	
Cohort I (1990–2001)						
Case	32	45	49	24	26	
Person-year	47978	64167	52043	40957	42814	
Multivariate-adjusted RR[a]	1.0	1.1	1.4	0.9	0.9	0.71
95% CI	(reference)	(0.7–1.7)	(0.9–2.2)	(0.5–1.6)	(0.5–1.6)	
Cohort II (1993–2001)						
Case	37	57	36	25	29	
Person-year	48088	60865	52201	47038	56523	
Multivariate-adjusted RR[a]	1.0	1.5	1.4	1.1	1.3	0.69
95% CI	(reference)	(0.96–2.3)	(0.8–2.2)	(0.6–1.9)	(0.7–2.2)	
Weighted mean estimates by the inverse of variance between Cohort I and II						
Case	69	102	85	49	55	
Person-year	96066	125031	104244	87995	99336	
Multivariate-adjusted RR[a]	1.0	1.3	1.4	1.0	1.1	0.98
95% CI	(reference)	(0.9–1.7)	(0.99–1.9)	(0.7–1.5)	(0.7–1.6)	

[a] Adjusted for age (continuous), Public Health Center areas, smoking (never, past, current), alcohol consumption (non-drinkers, 1–3 days/month, 1–149 g/week ethanol, 150–299 g/week, 300 or more g/week), body weight (quintiles).

cancer was attributable to 25 or higher BMI men compared with lower than 25 BMI men. With regard to subsite cancer, PAF estimates (95% CI) were 14% (3.7–23) for proximal colon cancer, 5.8% (−2.8 to 14) for distal colon cancer, and 2.4% (−6.7 to 11) for rectal cancer.

On the contrary, body height had no association with colorectal cancer in either sex of either cohort (Table 5). Site-specific colorectal cancer analyses also resulted in no association (data not shown). In addition, we calculated RRs for the highest decile category (173 cm or more in men and 159 cm or more in women) and the highest quartile category within the highest quintile category (175 cm or more in men, or 161 cm or more in women). However, these taller subjects were not associated with colorectal cancer either. Furthermore, we calculated stratified RRs by smoking, alcohol consumption, and body weight quintile category. No RR estimates by such analyses showed a significant association (data not shown).

Discussion

Colorectal cancer risk had a linear trend with increased BMI in the 25 or higher BMI men. Obese subjects (30 or higher BMI) showed the highest risk, although it was not statistically significant. These results were consistent with previous studies in both Western populations [2–4, 6–9, 12–15, 17] and Asian populations [25]. Although we hypothesized that even the 25–29.9 BMI subjects may be associated with a much elevated risk and may cause a rapid increase of colorectal cancer in the Japanese population, the RRs in such groups were not so high (1.2 for 25–26.9, 1.4 for 27–29.9). In other words, the relative effect of BMI was similar between Western and Asian populations. In addition, BMI's population-attributable fraction (PAF) was relatively small (6.7%) because of the small percentage of the 25 or higher BMI group. As a result, the PAF was too small to explain the increase in colorectal cancer incidence during recent decades.

The cancer risk similarly increased among proximal colon and distal colon. Proximal colon cancer, however, appeared to have a slightly stronger association with BMI than distal colon cancer. Many previous studies reported that BMI was strongly associated with distal colon cancer rather than proximal colon cancer [5, 8, 16, 17, 19]. A case-control study [47] revealed that high fat and protein intake were more closely associated with sigmoid colon cancer than ascending or transverse colon cancers. Thus, the association of BMI with site-specific colon cancer may differ among dietary lifestyles that lead to high BMI. Further studies may be needed in various populations with various dietary lifestyles, and in animal studies also, to clarify this site-specific association.

In addition, an association of BMI with colorectal cancer was clearer in only invasive-cancer cases rather than in overall colorectal-cancer cases including the non-invasive type. This result suggested that BMI may be associated with the promotion stage of carcinogenesis rather than the initiation stage [21, 26]. This hypothesis is also consistent with its stronger association with large adenoma rather than smaller adenoma [20–23, 26]. In other words, BMI may be related to cell proliferation and tumor growth in line with the insulin-like growth factor hypothesis [20]. High BMI as well as physical inactivity are hypothesized as factors that may lead to insulin resistance and high insulin and insulin-like growth factor concentration in blood, and then cause colorectal epithelial proliferation and carcinogenesis [3, 27]. Some epidemiologic evidence has been accumulated concerning an association between serum insulin or insulin-like growth factors and colorectal cancer by nested case-control studies [28].

In contrast, high BMI female subjects were not associated with colorectal cancer. Moreover, the association between BMI and colorectal cancer in women was inconsistent among previous studies [5, 6, 8, 10–17, 19, 24, 25]. Slattery *et al.* [14] hypothesized that estrogen-positive women (premenopausal women and postmenopausal women with hormone-replacement therapy) differed from estrogen-negative women (postmenopausal women without hormone-replacement therapy). Their result suggested that only estrogen-positive women were associated with an increased risk of colorectal cancer from being overweight or obese. Our further analyses stratified by age or menopausal status, however, did not support this hypothesis (data not shown). At least, women may have a weaker association than men in light of the present and previous studies.

The association of body height with colorectal cancer was inconsistent. Although previous cohort studies [4, 7, 9–11, 25] revealed this association, previous case-control studies failed to show any significant associations [15, 16, 18, 21]. Body height is hypothesized as a surrogate marker of a long large bowel [48] and a large number of colorectal epithelial cells. Such large numbers of cells carry a higher probability of carcinogenesis than smaller numbers of cells [49]. Another hypothesis is that a high caloric intake [49] and a high level of growth hormone in childhood may cause colorectal cell proliferation and carcinogenesis. Le Marchand *et al.* [50] reported that the genotype related to a low concentration of growth hormone in blood was inversely associated with colorectal cancer in a case-control study. However, our result suggested that body height was not associated

with colorectal cancer. Body height may have a threshold for colorectal carcinogenesis or a non-linear risk trend. Some studies [4, 9] reported a significant association of much greater body height, over 175 or 180 cm, with colon cancer in male populations. In these studies, the shortest height category ranged around 167 cm or less [4] or 68 in. (173 cm) or less [9], while in our study, even the highest category was only 170 cm or more in height. Therefore, body height may not be associated with colorectal cancer incidence unless it reaches 180 cm or more, though the proportion of men with a height of 180 cm or more was too small (0.5%) to examine this hypothesis in our study population.

The major strengths of our study include its prospective design, a general population with a high response rate (approximately 80%), and the relatively low proportion of subjects who moved away from the original study areas (9.6%) or were lost to follow-up (0.2%). Information on body height and body weight was collected before any subsequent diagnosis of colorectal cancer, thus avoiding the exposure recall bias inherent in case-control studies. The findings of this study can be generalized to middle-aged and elderly Japanese men and women because the study subjects were selected from the general population, and there was a high response rate. Moreover, the two cohorts starting at different times produced the same results. In addition, any confounding by factors measurable by our questionnaire was examined by the 10% change-in-estimate strategy and was excluded as thoroughly as possible. Although we used categorical variables of alcohol consumption and smoking as covariates to control confounding by these factors, our results did not substantially change when we used continuous variables of weekly ethanol intake and pack-years (number of cigarettes smoked per day divided by 20 and multiplied by years; data not shown in tables).

In conclusion, BMI increased the risk of colorectal cancer in men. Only invasive-cancer analysis suggested that BMI was important for tumor growth and proliferation. Proximal colon cancer appeared to have a slightly stronger association with BMI than distal colon cancer. Body height was not associated with colorectal cancer in men and women. From the risk estimates, 6.7% of colorectal cancer is attributable to a BMI of 25 or higher in middle-aged and elderly Japanese men.

Notes

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Short Communication

No association between fruit or vegetable consumption and the risk of colorectal cancer in Japan

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In a pooled analysis of two prospective studies with 88 658 Japanese men and women, fruit and vegetable consumptions, were not associated with a lower risk of colorectal cancer (705 cases); multivariate relative risk (95% confidence interval) for the highest *vs* the lowest quartile of intake being 0.92 (0.70–1.19) and 1.00 (0.79–1.27), respectively.
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Although fruit and vegetables have been suggested to confer protection against colorectal cancer, recent prospective studies in Western populations found no or limited associations (Michels *et al*, 2000; Voorrips *et al*, 2000). In Japan, mortality from colorectal cancer increased during 1950–2000, especially in men (age-adjusted rate per 100 000 of 2.9–14.4 for colon and 5.6–9.3 for rectum in men; 3.3–9.5 for colon and 4.2–4.1 for rectum in women) (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labor, and Welfare of Japan, 2003). Dietary factors may play a part in this increase, but the role of fruit and vegetables remains unclear. We therefore examined the association between fruit and vegetable consumption and the risk of colorectal cancer in the Japan Public Health Center (JPHC) prospective study on cancer and cardiovascular disease.

MATERIALS AND METHODS

The JPHC study has two population-based cohorts, and study designs are described in detail elsewhere (Otani *et al*, 2003). Briefly, Cohort I started in 1990 and included 40 106 subjects (19 345 men and 20 761 women) who were 40–59 years of age, lived in four Public Health Center districts, responded sufficiently to a self-administered questionnaire, and had no history of cancer (73.7% of the eligible subjects). Cohort II started in 1993 and included 48 552 subjects (23 180 men and 25 372 women) who were 40–69 years of age, lived in five Public Health Center districts, responded sufficiently to a self-administered questionnaire, and had no history of cancer (77.9% of the eligible subjects).

Cohort I questionnaire asked about the average consumption during the previous month of 44 food items including two fruit (fruit and fruit juice) and five vegetables (green leafy vegetables, yellow vegetables, white vegetables, pickled vegetables, and vegetable juice). Cohort II questionnaire asked about the average consumption during the previous month of 52 food items including three fruit (apples, oranges, and fruit juice) and six vegetables (green vegetables, carrot, tomatoes, green pickled vegetables, other pickled vegetables, and vegetable juice). The questionnaires had six frequency categories for fruit juice and vegetable juice that ranged from 'rarely' to '5 glasses day^{-1}', and four (Cohort I) or five (Cohort II) categories for other items that ranged from 'never' or 'rarely' to 'almost everyday'. The amount of consumption of total fruit and total vegetables (g day^{-1}) were calculated from these responses. We documented the questionnaire assessment of fruit and vegetable consumption to be reasonably valid (Kobayashi *et al*, 2002).

We followed up vital and residential status of subjects and incidence of cancer until the end of 1999. During 694 074 person-years of follow-up from the two cohorts, 705 cases of histologically confirmed colorectal cancer (456 colon and 249 rectum) were identified. Five percent of the subjects moved out of the study regions and 0.04% were lost to follow-up.

We used Cox's regression to compute from each cohort relative risk (RR) and 95% confidence interval (CI) of colorectal cancer according to quartiles of total fruit or vegetable consumption with adjustment for potential confounders. We pooled these estimates to obtain summary measures using inverse-variance weighting. As we observed no differential findings between the two cohorts, we present the pooled results only. This study has approximately 80% statistical power, with the two-sided α-error level of 5%, in detecting a true RR of 0.75 among the highest *vs* lowest quartiles of total vegetable consumption.

RESULTS

Compared with men in Cohort I in the lowest quartile of total vegetable consumption, men in the highest quartile were more likely to engage in sports and use vitamin supplements, less likely to be current smokers, and consumed higher amount of meats and fish, but lower amount of cereals. The men in the two groups did not differ with respect to age, body mass index, or the prevalence

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Table 1 Pooled multivariate RR and 95% CI of colorectal cancer for total fruit and total vegetable consumption[a]

	Quartiles of total fruit consumption					Quartiles of total vegetable consumption				
	Lowest	**Second**	**Third**	**Highest**	**Trend *P***	**Lowest**	**Second**	**Third**	**Highest**	**Trend *P***
Person-years in Cohort I	94 449	95 035	94 925	95 901		94 394	94 936	95 360	95 620	
Person-years in Cohort II	78 632	78 285	78 545	78 303		78 581	78 766	78 467	77 950	
Men and women										
Colorectum										
No. of cases	114/94	102/81	97/73	64/80		100/85	91/84	95/78	91/81	
RR (95% CI)	1.00	0.89	0.88	0.92 (0.70–1.19)	0.40	1.00	0.98	0.92	1.00 (0.79–1.27)	0.80
Colon										
No. of cases	77/56	70/51	66/48	43/45		67/50	60/53	68/44	61/53	
RR (95% CI)	1.00	0.89	0.93	0.92 (0.66–1.28)	0.61	1.00	0.99	0.96	1.08 (0.80–1.45)	0.73
Rectum										
No. of cases	37/38	32/30	31/25	21/35		33/35	31/31	27/34	30/28	
RR (95% CI)	1.00	0.88	0.78	0.91 (0.59–1.40)	0.47	1.00	0.95	0.84	0.87 (0.58–1.31)	0.37
Men										
Colorectum										
No. of cases	90/80	81/61	61/43	10/28		83/66	62/55	60/45	37/46	
RR (95% CI)	1.00	0.86	0.79	1.06 (0.70–1.61)	0.34	1.00	0.95	0.82	1.18 (0.88–1.59)	0.86
Colon										
No. of cases	59/51	57/36	42/31	8/16		57/40	42/36	41/27	26/31	
RR (95% CI)	1.00	0.83	0.86	1.02 (0.61–1.70)	0.57	1.00	0.96	0.84	1.24 (0.86–1.79)	0.69
Rectum										
No. of cases	31/29	24/25	19/12	2/12		26/26	20/19	19/18	11/15	
RR (95% CI)	1.00	0.91	0.68	1.19 (0.59–2.36)	0.42	1.00	0.91	0.81	1.06 (0.63–1.78)	0.81
Women										
Colorectum										
No. of cases	24/14	21/20	36/30	54/52		17/19	29/29	35/33	54/35	
RR (95% CI)	1.00	1.02	1.15	0.93 (0.61–1.42)	0.77	1.00	1.03	1.08	0.88 (0.57–1.35)	0.48
Colon										
No. of cases	18/5	13/15	24/17	35/29		10/10	18/17	27/17	35/22	
RR (95% CI)	1.00	1.07	1.19	0.87 (0.49–1.52)	0.86	1.00	1.09	1.25	1.01 (0.58–1.76)	0.96
Rectum										
No. of cases	6/9	8/5	12/13	19/23		7/9	11/12	8/16	19/13	
RR (95% CI)	1.00	0.77	0.95	0.84 (0.43–1.65)	0.77	1.00	0.96	0.84	0.71 (0.36–1.38)	0.27

RR = relative risk; CI = confidence interval. [a]RRs have been adjusted for sex, age (5-year groups), Public Health Centre area, body mass index in kg m^{-2} (less than 19, 19–22.9, 23–26.9, and 27 or more), frequency of sports (never or 1 day/month or more), smoking (never, past, and current), alcohol consumption (non, occasional, 1–149, 150–299, and 300 g week or more), vitamin supplement use, quartiles of energy, cereals, meats, and fish by each cohort. The lowest quartile serves as reference category. The numbers of colon and rectal cancers are from Cohort I/Cohort II.

of regular drinkers. We observed similar tendencies for women in Cohort I, and for men and women in Cohort II.

We found no significant association between fruit or vegetable intakes and the risk of colorectal cancer (Table 1). Multivariate RRs (95% CI) for the highest *vs* the lowest quartile of intake were 0.92(0.70–1.19) and 1.00(0.79–1.27), respectively, based on 705 cases. We observed no association whether or not colon and rectal cancers were separated, or men and women were separated. Exclusion of colorectal cancer cases diagnosed in the first 3 years of follow-up did not change the findings materially. Stratified analyses by covariates included in multivariate models did not reveal remarkable effect modifications. Analyses based on the octiles of total fruit or vegetable consumption did not show significant associations. No individual fruit or vegetables showed significant relations with risk.

DISCUSSION

This is the first prospective cohort study of fruit and vegetable consumption and incident risk of colorectal cancer in Japan. Our results are consistent with the recent prospective studies in Western populations showing no substantial protective associations (Michels *et al*, 2000; Voorrips *et al*, 2000).

Our food frequency questionnaires had relatively small number of fruit and vegetable items and limited range of frequency categories. Nevertheless, we had observed in Cohort I an inverse association between fruit and vegetable intakes and the risk of gastric cancer (Kobayashi *et al*, 2002). It is therefore unlikely that failure to observe protective association was due to the crude designs of our questionnaires.

While mortality from colorectal cancer in Japan increased during 1950–2000, the average consumption of fruit and vegetables also increased during this period (42–117 and 242–311 g day^{-1}, respectively) (Kenko Eiyo Joho Kenkyukai, 2002). Our results, along with these time trends, suggest that low consumption of fruit and vegetables is not primarily responsible for the increased rate of colorectal cancer in Japan.

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Appendix A

The members of the Japan Public Health Center-based Prospective Study (JPHC Study) Group are as follows: S Tsugane, M Inoue, T Sobue, T Hanaoka, National Cancer Center, Tokyo; J Ogata, S Baba, T Mannami, A Okayama, 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, Okinawa; 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, M Katagiri, 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, Japan.

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Reproductive factors, hormone use and the risk of lung cancer among middle-aged never-smoking Japanese women: A large-scale population-based cohort study

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Although a link between female hormonal factors and the risk of lung cancer has been suggested, few studies have examined this association in detail. We investigated the associations between reproductive factors, hormone use and the risk of lung cancer in a population-based prospective study. Self-administered questionnaires were distributed to 44,677 lifelong never-smoking women in 1990–1994 to assess menstrual and reproductive factors and hormone use. After 8–12 years of follow-up, 153 lung cancer cases were diagnosed. Relative risk (RR) and 95% confidence intervals (CI) were calculated using the Cox proportional hazards model. Age at menopause, age at menarche, number of children, age at first live birth, breast feeding and use of hormones were not associated with a risk of lung cancer, either overall or among postmenopausal women or women with natural menopause. Compared to women with both late age at menarche (≥16) and early age at menopause (≤50), those with either early age at menarche or late age at menopause had a >2-fold, significant increase in the risk of lung cancer. Induced menopausal women with experience of hormone replacement therapy had a significantly elevated risk compared to naturally menopausal women without female hormone use, with an RR of 2.40 (95% CI 1.07–5.40). These findings suggest that both endogenous and extraneous estrogen may be involved in the etiology of lung cancer.

Key words: age at menarche; induced menopause; hormone use; lung cancer; prospective study

A large body of research suggests an association between female hormonal factors and the risk of lung cancer in women. However, the results are quite inconsistent. With respect to early age at menopause, studies have variously shown no effect,[1–3] an increase[4] or a decrease[5,6] in risk; for late age at menarche, no significant effect[1–3,5,6] or a decrease in risk;[4] and for the use of hormones other than oral contraceptives, an increase,[3,6,7] a decrease[2,8,9] or no appreciable influence on risk. Laboratory data have also suggested that hormonal factors may be involved in the etiology of lung cancer. Estrogen (ER) and progesterone receptors (PR) were reported to be present in human lung cancers, and adenocarcinomas exhibited significantly higher expression than other lung cancer cell types.[10–12] The potential role of steroids in lung carcinogenesis by steroid receptor mediation[13] has led to the search for a hormonal role. To date, however, no study on the association between hormone factors and the risk of lung cancer has been reported from Japan, notwithstanding a low rate of smoking *vs.* a high and increasing incidence of lung cancer in Japanese women.[14] Moreover, data from prospective studies, with their inherently lower susceptibility to recall and selection bias, are scarce. To our knowledge, only one prospective study has been reported, which showed a moderately increased risk among women receiving hormone replacement therapy.[7]

Here, we investigated the association between hormonal factors (menstrual status, reproductive factors and hormone use) and the risk of lung cancer among never-smoking women in a population-based prospective study in Japan.

Material and methods

Study cohort

The Japan Public Health Center-based Prospective Study (JPHC Study) was launched with a population-based cohort in 1990 (Cohort I), then expanded with a second cohort in 1993–1994 (Cohort II). Subjects of Cohort I were recruited from among residents of 4 Public Health Center (PHC) areas and for Cohort II from 5 PHC areas. These 9 PHC areas were located in 9 prefectures distributed in Honshu, Kyushu and Shikoku and included 27 cities, towns and villages. Study subjects were all inhabitants with Japanese nationality who lived in the study areas at the start of the follow-up and were aged 40–59 in Cohort I and 40–69 in Cohort II. This population-based cohort of 116,694 subjects, among them 59,103 women (27,397 in Cohort I and 31,706 in Cohort II) were identified using population registries maintained by local governments. Details of the cohorts are described elsewhere.[15] Ethical approval was provided by the institutional review board of the National Cancer Center.

Baseline survey

A self-administered questionnaire, which included menstrual and reproductive history, hormone use, previous disease history and other lifestyle factors, was distributed to all eligible registered residents in 1990 for Cohort I and in 1993–1994 for Cohort II. Completed questionnaires were collected from 49,924 women, giving a response rate for women of 84%. We further excluded 7.3% of women with a past or current smoking habit and 1,302 women with a history of cancer at any site, leaving a total of 44,677 for analysis.

Menstrual and reproductive factors, hormone use

For both cohorts, the questions on reproductive history consisted of menstrual status, age at menarche, history of pregnancy and delivery and history of gender-specific disease (ovaritis, for example). Further data was collected from menopausal women on age and type of menopause (natural or induced). Information on female hormone use was also collected. The form of this question differed slightly between the 2 cohorts; Cohort I subjects were asked whether they had experience of using female hormone drugs, whereas Cohort II subjects were asked whether they had used female hormone drugs for contraception, the treatment of menstrual disorders or during menopause.

Follow-up

Subjects were followed until December 31, 2002. A total of 2,182 newly diagnosed cases of cancer were identified among the 44,677 never-smoking women, including 153 of lung cancer (118 adenocarcinomas, 20 others, 17 unknown). Cases of lung cancer occurring in the 2 cohorts were identified through continuous surveillance of hospital records, population-based cancer registries and death certificates. Site of origin and histologic type were

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TABLE I – DISTRIBUTION OF STUDY AND SOCIODEMOGRAPHIC VARIABLES FOR COHORTS I AND II

	Cohort I	Cohort II	Total
No. of subjects	20,115	24,562	44,677
Person-years	211,028	184,420	395,448
No. of cases	77	76	153
Adenocarcinoma	58	60	118
Others	12	8	20
Unknown	7	10	17
Family history of lung cancer (no. of subjects)	425	380	805
Mean BMI (kg/m^2)	24.1	24.1	24.1
Age at baseline (%)			
40–49 years	47.6	33.3	40.1
50–59 years	52.4	32.0	41.0
60–69 years	–	34.7	18.9
Alcohol drinking (%)			
< Once per week	76.4	79.6	78.2
Daily	2.4	3.5	3.0
Menopausal status (%)[1]			
Premenopausal	45.6	33.6	39.1
Natural menopause	45.9	57.2	52.0
Induced menopause	8.5	9.2	8.9
Hormone use (%)[2]	20.6	6.2	12.8
Postmenopausal women			
No. of subjects	10,732	15,465	26,197
Person-years	112,912	116,379	229,291
No. of cases	57	54	111
Adenocarcinoma	45	40	85
Family history of lung cancer (no. of subjects)	227	230	457
Mean BMI (kg/m^2)	24.2	24.2	24.2
Mean age at baseline			
Alcohol drinking (%)			
<Once per week	81.6	87.6	85.1
Daily	4.9	4.2	4.5
Hormone use (%)[3]	21.2	5.7	12.2

[1]1,643 women (387 in Cohort I, 1,256 in Cohort II) without data for menopausal status were excluded.–[2]3,324 women (1,222 in Cohort I, 2,002 in Cohort II) without data for hormone use were excluded.–[3]2,070 women (619 in Cohort I, 1,451 in Cohort II) without data for hormone use were excluded.

coded using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). Data on changes in residency were obtained from residential registries. Among noncase study subjects, 1,900 women (4.3%) moved out of the study area and only 0.04% were lost to follow-up within the study period. Death certificates collected through local public health centers revealed 811 deaths from causes other than lung cancer (1.8%) within the study period.

Statistical analysis

Person-years of follow-up were calculated for each subject from the start of the study until the date of diagnosis of lung cancer, date of migration out of the study area, date of death or the end of follow-up, whichever occurred first. The Cox proportional hazards model was used to estimate age-, PHC area- and passive smoking-adjusted and multivariate-adjusted relative risks (RR) for lung cancer. The assumption for the Cox proportional hazards model has been checked by graphical assessment and found to be valid. The effect of interaction was assessed by the likelihood ratio test. Records with missing information in the corresponding categories were deleted. Passive smoking in the workplace was defined as occurring when a woman inhaled other people's smoke for more than 1 hr per day on at least 1 day per week. Women who had family members with a smoking habit when the woman was in her childhood or adolescence were classified as having experienced passive smoking during childhood. Multivariate-adjusted relative risk included further adjustment for the confounding factors of sports in leisure time (<1 time/week, 1+ time/week), alcohol consumption (nondrinker, ≤2 days/week, 3+ days/week), body mass index (<20.0, 20.0–24.9, 25.0+), green and yellow vegetable consumption (<1 day/week, 1–4 days/week, almost daily) and family history of lung cancer (no, yes). Covariates were treated as categorical variables with indicator variables representing the categories. All computations were performed using the SAS software package version 8 (SAS Institute, Cary, NC)

Results

Table I shows the baseline information and characteristics of the 2 cohorts. Because Cohort I recruited women aged 40–59 and Cohort II recruited those aged 40–69, the percentage of postmenopausal women was higher in Cohort II, whereas the percentages of induced menopausal women were similar. No difference was seen between the cohorts in the proportion of adenocarcinoma, body mass index or alcohol drinking habit. The only difference between them except age was the percentage of hormone use, with fewer women receiving hormone therapy in Cohort II. This difference was consistent across all age groups (5-year strata).

Lung cancer risk according to reproduction-related factors and hormone use among never-smoking women is shown in Table II. None of the menstrual or reproductive variables analyzed showed a statistically significant association with lung cancer. A moderately increased risk was observed among induced menopausal women compared to premenopausal or naturally menopausal women. Breast feeding also seemed related to increased risk, whereas early age at menopause (≤50) showed a slightly decreased risk among naturally menopausal women. Hormone use and age at first birth of ≥23 years were associated with an elevated risk among postmenopausal women, although risk decreased toward null when analysis was restricted to naturally menopausal women. No association between risk of lung cancer and variables was seen with regard to age at menarche or parity. Duration of menstruation among naturally menopausal women was

TABLE II – RELATIVE RISK (RR) AND 95% CONFIDENCE INTERVALS (CI) OF LUNG CANCER ACCORDING TO REPRODUCTION-RELATED FACTORS AND HORMONE USE AMONG NEVER-SMOKING WOMEN[1]

	No. of subjects	No. of cases	Person-years	RR (95% CI)	Postmenopausal			
					All		Natural	
					No. of cases	RR (95% CI)	No. of cases	RR (95% CI)
Menopausal status								
Premenopausal	16,837	30	152,735	1.00				
Natural menopausal	22,381	92	195,772	1.11 (0.61–2.02)	92	1.00	–	–
Induced menopausal	3,816	19	33,519	1.62 (0.83–3.17)	19	1.45 (0.86–2.44)	–	–
Hormone use								
No	36,077	113	315,628	1.00	83	1.00	72	1.00
Yes	5,276	24	50,938	1.46 (0.92–2.32)	18	1.45 (0.84–2.49)	11	1.13 (0.58–2.23)
Breast feeding								
No	4,964	10	44,561	1.00	6	1.00	4	1.00
Yes	34,612	122	306,949	1.64 (0.83–3.25)	89	1.60 (0.70–3.67)	74	1.86 (0.68–5.11)
Age at menarche (years)								
≤13	10,423	23	92,599	1.00	13	1.00	9	1.00
14–15	19,805	72	176,038	1.13 (0.70–1.83)	53	1.17 (0.63–2.16)	46	1.29 (0.63–2.65)
≥16	13,087	51	114,075	0.84 (0.48–1.45)	41	0.79 (0.41–1.53)	34	0.80 (0.37–1.72)
Age at menopause (years)								
≥51	8,182	45	71,038	–	43	1.00	41	1.00
46–50	12,753	47	111,760	–	40	0.61 (0.34–0.95)	38	0.64 (0.41–1.01)
≤45	5,486	26	47,765	–	26	1.02 (0.62–1.69)	11	0.79 (0.41–1.55)
Years of menstruation								
≤30	6,195	31	53,498	–	31	1.00	17	1.00
31–35	11,467	35	100,551	–	35	0.89 (0.53–1.48)	32	1.38 (0.68–2.79)
≥36	8,337	39	72,223	–	39	1.08 (0.64–1.82)	38	1.71 (0.83–3.50)
Parity								
0–2	18,804	56	166,201	1.00	40	1.00	31	1.00
3–4	17,845	61	160,488	0.94 (0.64–1.37)	46	0.96 (0.62–1.50)	38	0.92 (0.56–1.51)
≥5	5,217	20	44,530	0.95 (0.53–1.71)	14	0.86 (0.43–1.71)	13	0.82 (0.39–1.70)
Age at first live birth								
≤22	9,327	22	83,235	1.00	16	1.00	15	1.00
23–25	15,963	56	141,647	1.43 (0.87–2.38)	38	1.49 (0.82–2.70)	32	1.30 (0.69–2.44)
≥26	13,658	54	122,062	1.50 (0.90–2.51)	41	1.65 (0.91–3.01)	31	1.23 (0.65–2.34)

[1]Adjusted for age, public health center (PHC) area, and passive smoking during childhood or in the workplace.

moderately related with risk, but the results and *p*-value for the trend were not statistically significant.

Table III shows lung cancer risk according to age at menarche and menopause among postmenopausal women. Compared to women with both late age at menarche (≥16) and early age at menopause (≤50), those with early age at menarche or late age at menopause had a ≥ 2-fold, significantly increased risk of lung cancer. The *p*-value for interaction was 0.08, suggesting the existence of a moderate level of negative interaction. Risk did not change materially but slightly increased when analysis was restricted to naturally menopausal women or when further adjustment for hormone use was made.

We further evaluated the interaction between hormone use and induced menopause relative to the risk of total lung cancer and adenocarcinoma of the lung (Table IV). In comparison to naturally menopausal women who had no experience of hormone use, hormone use alone and induced menopause alone were not related to the risk of total lung cancer or adenocarcinoma tumor. Induced menopausal women who had experience of hormone use, however, had a significantly elevated risk of total lung cancer and adenocarcinoma, with RR values of 2.40 (95% CI 1.07–5.40) and 2.71 (95% CI 1.12–6.58), respectively. Tests for interaction were not significant, with *p*-values of 0.34 and 0.41, respectively. Results for hormone use and induced menopause relative to the risk of total lung cancer and adenocarcinoma did not change substantially when the 2 cohorts were analyzed separately.

Further adjustment for lung cancer family history, alcohol drinking habit, green and yellow vegetable consumption and physical activity during leisure time did not alter the results appreciably.

TABLE III – RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) OF LUNG CANCER ACCORDING TO AGE OF MENARCHE AND MENOPAUSE AMONG POSTMENOPAUSAL NEVER-SMOKING WOMEN[1]

Age at menopause	Age at menarche		*P*-value for interaction
	≥16 years (case/person-years)	≤15 years (case/person-years)	
≤50 years	18/60,343	44/90,896	
	1.00	2.15 (1.18–3.91)	
>51 years	22/30,411	21/36,886	
	2.49 (1.30–4.79)	2.20 (1.13–4.29)	0.08
Natural menopausal women			
≤50 years	13/52,473	33/69,265	
	1.00	2.38 (1.19–4.75)	
≥51 years	20/29,857	21/35,722	
	2.62 (1.27–5.42)	2.76 (1.32–5.77)	0.03

[1]Adjusted for age, public health center (PHC) areas, passive smoking at the workplace and during childhood.

Discussion

In our study, no statistically significant association was observed between age at menopause, age at menarche, number of children, age at first live-birth, breast feeding or use of hormones and the risk of lung cancer, either overall or among postmenopausal women or women with natural menopause. Although previous studies have examined variables in terms of age at menarche or menopause, as well as hormone use, the combined effects of these variables on the risk of lung cancer have not been evaluated. When we calculated and divided total years of menstruation of naturally menopausal women into 3 categories (<30, 31–35, ≥36 years) and examined associations with lung cancer risk, a positive but not statistically significant association with length of menstruation was suggested. Furthermore, although late age at menarche and early age at menopause were not individually associated with a significantly reduced risk of lung cancer, their combination was associated with a remarkably lowered risk. It is therefore possible that the length of exposure to estrogen at least partly accounts for the risk of lung cancer.