green tea intake (none, less than daily, daily) were also included. These variables are either known or suspected risk factors for cancer or had previously been found to be associated with the risk of liver cancer. Tests for linear trend in risk of HCC were assessed by assigning ordinal exposure variables as continuous terms. The HR were estimated both for men and women combined and for men and women separately. Stratified analyses were conducted to evaluate whether the association between coffee drinking and the risk of HCC varied with age, smoking status, weekly ethanol intake, green vegetable intake, green tea drinking, and past or present history of chronic liver disease. Interaction terms were generated by multiplying ordinal exposure variables by ordinal coffee-drinking categories. Because no statistically significant effect modifications were found between sex and coffee drinking ($P_{interaction}$ = .81), men and women were combined in the stratified analyses. Stata software (version 8.0) *(17)* was used to perform the statistical analyses. All statistical tests were two-sided.

Results

During 874 551 person-years of follow-up (average follow-up period: 9.7 years) of 90 452 subjects (43 109 men and 47 343 women), a total of 334 participants were newly diagnosed with HCC (250 men and 84 women). Information on the hepatitis virus infection status of the patients was available for 259 (77.5%) of the case patients. Among these 259 case patients, 164 (63.3%) were HCV positive and 60 (23.2%) were HBV positive (Table 1).

The baseline characteristics of the study subjects according to coffee consumption are shown in Table 2. Coffee was consumed almost every day by 37.1% of the subjects in the study. No substantial difference in the distribution of coffee intake frequency was observed between men and women. The proportion of current smokers increased as coffee intake increased in both sexes. However, alcohol intake increased in women and decreased in men as coffee intake increased. Frequent green vegetable intake and daily green tea drinking decreased in both sexes with increased coffee drinking. The proportion of subjects with a self-reported present/past history of chronic hepatitis and/or cirrhosis among the study subjects overall was 0.3%–3% across the coffee intake categories.

Table 1. Status of hepatitis virus infection among incident cases of hepatocellular carcinoma (HCC)*

	Total	Men	Women
Characteristic	N (%)	N (%)	N (%)
Total	334	250	84
Case patients with information on hepatitis virus infection	259 (77.5)†	194 (77.6)†	65 (77.4)†
HCV+	164 (63.3)‡	119 (61.3)‡	45 (69.2)‡
HBV+	60 (23.2)‡	42 (21.6)‡	18 (27.7)‡
Both HCV and HBV−	43 (16.6)‡	39 (20.1)‡	4 (6.1)‡
HCV+, HBV−	156 (60.2)‡	113 (58.2)‡	43 (66.2)‡
HBV+, HCV−	52 (20.1)‡	36 (18.6)‡	16 (24.6)‡
Both HCV and HBV+	8 (3.1)‡	6 (3.1)‡	2 (3.1)‡

*Data are based on 334 newly diagnosed case patients with HCC among 90 452 Japanese men and women aged 40–69 years at baseline followed up for 10 years (JPHC Study).

†Percentage of total.

‡Percentage among case patients with information on hepatitis.

The minimally adjusted and multivariable HR for the subsequent occurrence of HCC according to baseline coffee-drinking categories are presented in Table 3. Coffee drinking was associated with a statistically significantly lower risk for HCC. Subjects who drank coffee almost every day had a 51% lower HCC risk than those who almost never drank (HR = 0.49, 95% CI = 0.36 to 0.66), and the risk was inversely proportional to coffee intake (for 1–2 cups per day compared with no coffee intake, HR = 0.52; for 3–4 cups per day, HR = 0.48; for ≥5 cups per day, HR = 0.24; P_{trend}<.001). The risk of liver cancer in almost never drinkers in this population over 10 years of follow-up was 547.2 cases per 100 000 people. In contrast, the risk with drinking coffee almost everyday dropped to 214.6 cases per 100 000 people over the same follow-up time, 227.3 with drinking 1–2 cups per day, 205.0 with 3–4 cups per day, and 120.7 with ≥5 cups per day, respectively. Similar results were also observed in separate analyses by sex. Furthermore, when patients were analyzed according to hepatitis virus infection status, an inverse association between coffee drinking and HCC risk was observed for those who were HCV positive; however, the trend was not statistically significant for those who were HBV positive.

The inverse association between HCC risk and coffee intake persisted when participants were stratified by age, smoking status, ethanol intake, green vegetable intake, and green tea drinking (Table 4). Thus, the inverse association between coffee drinking and HCC risk is independent of these lifestyle factors. An inverse but weaker association was also observed in analyses of participants stratified by history of chronic hepatitis or cirrhosis.

We explored other possible confounders that could explain the observed association between coffee drinking and HCC, because coffee drinking is associated with many other factors. Socioeconomic status could not be assessed because of a lack of information in the questionnaire. Among the dietary factors that were examined, bread intake was positively associated with coffee drinking. However, no association was found between bread intake and HCC, and the results remained essentially unchanged when bread intake was included in the model (data not shown).

Discussion

In this prospective analysis of a large-scale population-based cohort study in Japan, a statistically significant inverse association between coffee drinking and HCC was observed. The results from the present study are consistent with but more pronounced than those of previous studies *(7–9)*. The risk of liver cancer in almost never drinkers in this population was 547.2 cases per 100 000 people over 10 years, but it was 214.6 cases per 100 000 people with drinking coffee on a daily basis.

The strength of the present study is its population-based prospective design with low proportion of losses to follow-up. Nonetheless, there are some obvious limitations, such as the assessment of coffee intake solely on the basis of the self-report at a single time point and lack of determination of hepatitis virus infection status at baseline for the entire population and at follow-up for 22% of the case patients.

Information on coffee intake was collected before subsequent diagnoses of cancer, thereby avoiding the exposure recall bias that is inherent to case–control studies. Study subjects were selected from the general population, and the response rate of 82% to the baseline questionnaire is acceptable for such a study

Table 2. Baseline characteristics of the study subjects according to coffee intake*

Category		Coffee intake						
					Almost everyday			
		Almost never	1-2 days/week	3-4 days/week	1-2 cups/day	3-4 cups/day	≥5 cups/day	$P_{difference}$†
Total (n = 90 452)								
No. of subjects		29 423	17 159	10 316	23 753	7316	2485	
Proportion, %		32.5	19.0	11.4	26.3	8.1	2.7	
Age, years ± SD		54.3 ± 7.7	52.7 ± 7.7	51.2 ± 7.7	50.2 ± 7.6	47.9 ± 7.0	48.6 ± 7.3	<.001
Person-years		285 446	166 876	101 215	228 995	68 733	23 286	
Smoking status	Current smokers, %	22.7	25.2	28.6	29.1	44.4	55.4	<.001
Ethanol intake	Weekly or more, %	36.7	37.3	39.9	37.5	41.7	39.6	<.001
Green vegetable intake	≥3 times/week, %	65.1	63.3	65.4	63.4	58.0	56.4	<.001
Green tea drinking	Everyday, %	76.1	77.5	73.6	74.5	68.2	65.8	<.001
Present/past history of chronic hepatitis/cirrhosis, %		2.1	1.4	1.1	1.1	1.2	1.3	<.001
Men (n = 43 109)								
No. of subjects		13 584	8096	5162	10 718	4033	1516	
Proportion, %		31.5	18.8	12.0	24.9	9.3	3.5	
Age, y ± SD		53.5 ± 7.7	52.4 ± 7.7	51.2 ± 7.7	50.5 ± 7.5	48.4 ± 7.2	48.8 ± 7.4	<.001
Person-years		130 225	77 913	50 133	101 211	37 309	14 009	
Smoking status	Current smokers, %	44.1	49.0	52.7	56.5	69.7	76.4	<.001
Ethanol intake	Weekly or more, %	69.9	69.1	69.4	67.9	62.6	55.4	<.001
Green vegetable intake	≥ 3 times/week, %	60.6	57.8	60.8	57.6	52.7	52.3	<.001
Green tea drinking	Everyday, %	75.4	76.1	72.8	74.5	69.9	65.2	<.001
Present/past history of chronic hepatitis/cirrhosis, %		3.0	2.1	1.7	1.7	1.7	1.9	<.001
Women (n = 47 343)								
No. of subjects		15 839	9063	5154	13 035	3283	969	
Proportion, %		33.5	19.1	10.9	27.5	6.9	2.1	
Age, years ± SD		55.0 ± 7.7	52.9 ± 7.7	51.3 ± 7.7	49.9 ± 7.5	47.3 ± 6.6	48.3 ± 7.2	<.001
Person-years		155 221	88 963	51 082	127 784	31 424	9277	
Smoking status	Current smokers, %	4.3	4.0	4.4	6.5	13.2	22.6	<.001
Ethanol intake	Weekly or more, %	8.6	9.4	10.8	12.7	16.0	15.1	<.001
Green vegetable intake	≥ 3 times/week, %	68.9	68.2	70.0	68.2	64.5	62.8	<.001
Green tea drinking	Everyday, %	76.8	78.8	74.4	74.5	66.2	66.6	<.001
Present/past history of chronic hepatitis/cirrhosis, %		1.3	0.9	0.5	0.7	0.5	0.3	<.001

*Data are based on 90 452 Japanese men and women aged 40–69 years at baseline followed up for 10 years (JPHC Study).

†$P_{difference}$ values of characteristics between categories of coffee intake (two-sided) were calculated by analysis of variance and chi-square test for homogeneity.
SD = standard deviation.

setting. The proportion of losses to follow-up (0.05%) was negligible during the study period. However, because self-reported information on coffee intake was used in the present study, some misclassification may have been unavoidable. Also, changes in coffee intake that arose from symptoms related to a subsequent diagnosis of HCC after the start of the study may have resulted in some misclassification. Such misclassification, if any, is probably nondifferential and would lead to an underestimation of the results. Although the quality of the cancer registry system was satisfactory over the study period, some variations in quality between the study areas occurred. The study areas used in the analysis were adjusted to control for geographic variation. The quality of the registry system was not affected by the coffee intake status; therefore, possible misclassification of cancer occurrence by an underreporting of cancer diagnosis would be nondifferential and would also bias the results toward the null.

The inverse association between coffee drinking and HCC has been investigated from various aspects. Coffee contains large amounts of antioxidants, including chlorogenic acid, and several animal studies have shown that such coffee compounds have a direct inhibitory effect or a lack of carcinogenic potential in the liver *(6,18)*. Caffeine is another major ingredient of coffee *(5)*. In this study, the type of coffee consumed was not classified as either decaffeinated or caffeinated because this information was not included in the questionnaire. However, decaffeinated coffee is rarely consumed in Japan. Thus, based on the limited information in our population, we cannot determine whether the inverse association with coffee is mainly attributable to caffeine. Green tea is another major source of caffeine intake in the Japanese population. However, in additional analyses using the same data set, no association between green tea intake and the risk of HCC was observed (data not shown). Green tea contains large amounts of antioxidant catechins. The differences in the antioxidant components of coffee and tea may explain the different associations of these beverages with liver cancer. One study comparing the antioxidant activity of coffee and tea indicated that, on a per-cup basis, soluble coffee has higher antioxidant activity than green tea *(19)*. Other unidentified substances in coffee may also be responsible for the observed association between coffee drinking and the risk of HCC. In any case, site specificity of the effect of coffee is another important issue that must be solved.

Coffee-drinking habits were associated with habitual tobacco smoking and alcohol drinking in our study population. However, the association between coffee intake and subsequent risk of HCC persisted even after adjustment for smoking and alcohol intake. Also, separate analyses performed according to smoking and alcohol drinking status showed a similar reduced risk, without substantial effect modification by coffee drinking.

Several studies have described an inverse association between coffee drinking and liver cirrhosis *(20–22)*. Because liver cirrhosis is strongly associated with primary liver cancer *(23)*, it is possible

Table 3. Hazard ratio (HR) and 95% confidence interval (CI) for hepatocellular carcinoma (HCC) according to coffee drinking*

	Coffee intake							
				Almost everyday				
Category (n)	Almost never	1-2 days/week	3-4 days/week	Total	1-2 cups/day	3-4 cups/day	≥5 cups/day	P_{trend}
Men and women combined (334)								
Person-years	285 446	166 876	101 215	321 014	228 995	68 733	23 286	
No. of case patients	161	65	36	72	54	15	3	
HR (95% CI)†	1.00	0.75 (0.56 to 0.998)	0.75 (0.52 to 1.08)	0.53 (0.39 to 0.70)	0.56 (0.41 to 0.77)	0.51 (0.30 to 0.88)	0.27 (0.09 to 0.85)	<.001
Multivariable HR (95% CI)‡	1.00	0.75 (0.56 to 1.01)	0.79 (0.55 to 1.14)	0.49 (0.36 to 0.66)	0.52 (0.38 to 0.73)	0.48 (0.28 to 0.83)	0.24 (0.08 to 0.77)	<.001
Men (250)								
Person-years	130 225	77 913	50 133	152 528	101 211	37 309	14 009	
No. of case patients	116	43	27	59	45	11	3	
HR (95% CI)†	1.00	0.74 (0.53 to 1.03)	0.72 (0.47 to 1.10)	0.54 (0.39 to 0.75)	0.61 (0.43 to 0.86)	0.44 (0.24 to 0.83)	0.31 (0.10 to 0.98)	<.001
Multivariable HR (95% CI)‡	1.00	0.74 (0.52 to 1.05)	0.76 (0.50 to 1.16)	0.49 (0.35 to 0.69)	0.55 (0.38 to 0.80)	0.41 (0.21 to 0.77)	0.27 (0.09 to 0.87)	<.001
Women (84)								
Person-years	155 221	88 963	51 082	168 486	127 784	31 424	9277	
No. of case patients	45	17	9	13	9	4	0	
HR (95% CI)†	1.00	0.78 (0.45 to 1.38)	0.85 (0.41 to 1.75)	0.46 (0.24 to 0.88)	0.41 (0.19 to 0.86)	0.88 (0.30 to 2.56)		.029
Multivariable HR (95% CI)‡	1.00	0.77 (0.43 to 1.37)	0.89 (0.43 to 1.84)	0.48 (0.25 to 0.92)	0.43 (0.20 to 0.90)	0.89 (0.31 to 2.59)		.042
HCC with HCV+ (164) (men and women combined)								
No. of case patients	86	26	15	37	29	6	2	
HR (95% CI)†	1.00	0.57 (0.37 to 0.89)	0.64 (0.37 to 1.11)	0.60 (0.40 to 0.89)	0.66 (0.43 to 1.03)	0.45 (0.19 to 1.05)	0.37 (0.09 to 1.53)	.007
Multivariable HR (95% CI)‡	1.00	0.59 (0.38 to 0.91)	0.66 (0.38 to 1.16)	0.57 (0.37 to 0.86)	0.64 (0.41 to 0.99)	0.42 (0.18 to 0.99)	0.34 (0.08 to 1.41)	.005
HCC with HBV+ (60) (men and women combined)								
No. of case patients	24	9	9	18	12	5	1	
HR (95% CI)†	1.00	0.65 (0.30 to 1.40)	1.10 (0.51 to 2.38)	0.72 (0.38 to 1.36)	0.70 (0.34 to 1.43)	0.88 (0.33 to 2.39)	0.44 (0.06 to 3.32)	.431
Multivariable HR (95% CI)‡	1.00	0.66 (0.31 to 1.43)	1.14 (0.52 to 2.47)	0.60 (0.31 to 1.18)	0.56 (0.26 to 1.21)	0.81 (0.30 to 2.22)	0.39 (0.05 to 2.98)	.231
HCC with HCV− and HBV− (43) (men and women combined)								
No. case patients	22	10	4	7	7	0	0	
HR (95% CI)†	1.00	0.83 (0.39 to 1.75)	0.55 (0.19 to 1.61)	0.33 (0.14 to 0.80)	0.47 (0.20 to 1.11)			.006
Multivariable HR (95% CI) ‡	1.00	0.87 (0.41 to 1.87)	0.57 (0.19 to 1.70)	0.36 (0.15 to 0.87)	0.50 (0.20 to 1.20)			.010

*Data are based on 90 452 Japanese men and women aged 40–69 years at baseline followed up for 10 years (JPHC Study).

†HR adjusted for sex (men and women combined analysis only), age (3-year age categories) and study area (nine public health centers).

‡Multivariable HR adjusted for sex (men and women combined analysis only), age (3-year age categories), study area (nine public health centers), tobacco-smoking status (never, former, current), ethanol intake (non- and ex-drinkers, less than weekly, weekly or more [<150 g/week, ≥150 g/week]), green vegetable intake (<3 times/week, 3–4 times/week, everyday), and green tea drinking (none, less than everyday, everyday).

Table 4. Hazard ratios (HR) and 95% confidence intervals (CI) for hepatocellular carcinoma (HCC) stratified according to selected lifestyle factors*

Characteristic	Multivariable HR (95% CI) by coffee intake								
				Almost everyday					
	Almost never	1-2 days/week	3-4 days/week	Total	1-2 cups/day	3-4 cups/day	≥5 cups/day	P_{trend}	$P_{interaction}$
Age, years									.85
<55	1.00	1.05 (0.61 to 1.78)	0.82 (0.42 to 1.59)	0.58 (0.35 to 0.97)	0.60 (0.34 to 1.06)	0.59 (0.26 to 1.31)	0.39 (0.09 to 1.64)	.021	
≥55	1.00	0.65 (0.45 to 0.93)	0.82 (0.52 to 1.27)	0.47 (0.32 to 0.69)	0.51 (0.34 to 0.78)	0.45 (0.21 to 0.98)	0.16 (0.02 to 1.12)	<.001	
Smoking									.10
Never/former	1.00	0.80 (0.54 to 1.18)	1.07 (0.68 to 1.69)	0.62 (0.41 to 0.93)	0.58 (0.37 to 0.91)	0.88 (0.44 to 1.78)	0.34 (0.05 to 2.43)	.050	
Current	1.00	0.68 (0.43 to 1.07)	0.50 (0.27 to 0.93)	0.4 (0.25 to 0.62)	0.47 (0.29 to 0.76)	0.29 (0.12 to 0.67)	0.22 (0.05 to 0.91)	<.001	
Ethanol intake									.54
Non- or ex-drinker/less than weekly	1.00	0.80 (0.54 to 1.18)	0.78 (0.47 to 1.29)	0.45 (0.30 to 0.68)	0.41 (0.25 to 0.67)	0.66 (0.34 to 1.27)	0.29 (0.07 to 1.20)	<.001	
Weekly or more	1.00	0.67 (0.42 to 1.06)	0.77 (0.45 to 1.32)	0.53 (0.34 to 0.82)	0.64 (0.41 to 1.01)	0.28 (0.10 to 0.77)	0.19 (0.03 to 1.41)	.002	
Green vegetable intake, per week									.66
<3	1.00	0.75 (0.48 to 1.19)	0.71 (0.39 to 1.27)	0.55 (0.36 to 0.86)	0.59 (0.36 to 0.95)	0.54 (0.26 to 1.13)	0.31 (0.07 to 1.28)	.006	
≥3	1.00	0.75 (0.51 to 1.11)	0.85 (0.53 to 1.36)	0.43 (0.28 to 0.67)	0.47 (0.30 to 0.75)	0.41 (0.17 to 0.94)	0.17 (0.02 to 1.24)	<.001	
Green tea intake									.40
Less than everyday	1.00	0.57 (0.34 to 0.96)	0.74 (0.42 to 1.30)	0.52 (0.34 to 0.80)	0.58 (0.36 to 0.92)	0.41 (0.19 to 0.93)	0.32 (0.08 to 1.32)	.003	
Everyday	1.00	0.83 (0.58 to 1.20)	0.78 (0.49 to 1.26)	0.45 (0.29 to 0.68)	0.46 (0.29 to 0.74)	0.52 (0.25 to 1.09)	0.16 (0.02 to 1.14)	<.001	
Past history of chronic hepatitis/cirrhosis									.17
Absent	1.00	0.85 (0.59 to 1.24)	1.15 (0.76 to 1.74)	0.45 (0.30 to 0.67)	0.46 (0.29 to 0.72)	0.52 (0.26 to 1.05)	0.15 (0.02 to 1.05)	<0.001	
Present	1.00	0.79 (0.48 to 1.30)	0.44 (0.18 to 1.11)	0.91 (0.58 to 1.41)	0.99 (0.61 to 1.61)	0.71 (0.31 to 1.67)	0.76 (0.18 to 3.16)	0.432	

*HR adjusted for sex (men and women combined analysis only), age (3-year age categories), study area (nine public health centers), tobacco-smoking status (never, former, current), ethanol intake (non- and ex-drinkers, less than weekly, weekly or more [<150 g/week, ≥150 g/week]), green vegetable intake (<3 times/week, 3-4 times/week, everyday), and green tea drinking (no, less than everyday, everyday), other than the variable for stratification.

that the observed association between coffee drinking and HCC actually represents an association with liver cirrhosis. In addition, an inverse association between coffee and alcoholic but not non-alcoholic cirrhosis has been reported *(18)*, and other cross-sectional observations have suggested an inhibitory effect of coffee on the alcohol-related increase in serum liver enzymes, such as aminotransferase and gamma-glutamyltransferase *(24–26)*. However, because a previous study found that caffeine metabolism was impaired in fasting subjects with liver cirrhosis, subjects with chronic liver disease may have reduced their coffee consumption to avoid the side effects of caffeine *(27)*, and that may have led to a superficial decrease in HCC risk by coffee drinking. One limitation of the present study is that we determined whether the subjects with chronic liver disease who did not drink coffee at baseline had quit drinking coffee after their chronic liver disease emerged. However, because a recent case–control study reported a strong association between coffee drinking and HCC among patients with HCV-associated chronic liver disease *(28)*, it is still possible to speculate that coffee drinking reduces the risk of HCC even after acquisition of a chronic liver disease. In any case, potential targets of coffee, HCC, liver cirrhosis, or both conditions, and whether a restriction to alcohol-related conditions exists, remain to be determined in future studies.

In addition, the lower risk associated with coffee intake among HCC case patients with HCV infections was somewhat stronger than that for HCC case patients with HBV infections, although these observations are not sufficient to confirm viral specificity for the association with coffee on the carcinogenesis of HCC. During hepatocarcinogenesis, direct integration of the viral sequence into the host genome is thought to substantially increase genomic instability in HBV-associated HCC, whereas the reaction of the host immune system against virus-infected cells is more important to the development of HCV-associated HCC *(29)*. Furthermore, it is also possible that the difference in the association according to virus infection status is attributed to differences between HBV-induced hepatocarcinogenesis and HCV-induced hepatocarcinogenesis. In this study, the virus infection status at baseline was not determined for the entire population, thus preventing clarification of a relationship between coffee drinking and HCC risk among subjects who are positive for each virus infection. Moreover, information on the virus infection status was not available for 22% of the case patients; most of the missing information resulted from the deletion of stored medical records after expiration of their holding period. Although a previous study analyzed the effect of coffee on the risk of HCC according to the hepatitis status of the subjects and reported a lower risk in those who drank coffee frequently than in those who drank it infrequently among both hepatitis-positive and -negative subjects *(9)*, risk differences according to the type of hepatitis virus infection have not been determined.

The present cohort analysis confirmed a statistically significant inverse association between habitual coffee drinking and HCC (that was not due to any confounders we analyzed). Further studies are warranted to assess whether the present results can be generalized to or are representative of other populations.

References

(1) Ferlay J, Bray F, Pisani P, Parkin DM. Globocan2000: Cancer incidence, mortality and prevalence worldwide. Vol 1.0. IARC Cancer Base, No. 5. Lyon (France): IARC Press; 2001.

(2) Pisani P, Parkin DM, Munoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. Cancer Epidemiol Biomarkers Prev 1997;6:387–400.

(3) World Cancer Research Fund /American Institute for Cancer Research. Food, nutrition and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 1997.

(4) International Agency for Research on Cancer. Coffee, tea, mate, methylxanthines, and methylgloxyal. IARC Monogr Eval Carcinog Risks Hum 1991:51:41–206.

(5) All Japan Coffee Association. Biannual report of the trend survey of coffee in Japan. Tokyo (Japan): All Japan Coffee Association, 2003.

(6) Tanaka T, Nishikawa A, Shima H, Sugie S, Shinoda T, Yoshimi N, Iwata H, Mori H. Inhibitory effects of chlorogenic acid, reserpine, polyprenoic acid (E-5166), or coffee on hepatocarcinogenesis in rats and hamsters. Basic Life Sci 1990;52:429–40.

(7) Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, Trichopoulos D, Stuver SO. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. Int J Cancer 2000;85:498–502.

(8) La Vecchia C, Ferraroni M, Negri E, D'Avanzo B, Decarli A, Levi F, Franceschi S. Coffee consumption and digestive tract cancers. Cancer Res 1989;49:1049–51.

(9) Gallus S, Bertuzzi M, Tavani A, Bosetti C, Negri E, La Vecchia C, Lagiou P, Trichopoulos D. Does coffee protect against hepatocellular carcinoma? Br J Cancer 2002;87:956–9.

(10) Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, Teratani T, Tohgo G, Toda N, Ohashi M, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B- and C- viral infection in Japan. Hepatology 1995;22:1027–33.

(11) Tanaka Y, Hanada K, Mizokami M, Yeo AE, Shih JW, Gojobori T, Alter HJ. A comparison of the molecular clock of hepatitis C virus in the United States and Japan predicts that hepatocellular carcinoma incidence in the United States will increase over the next two decades. Proc Natl Acad Sci U S A 2002;99:15584–9.

(12) Omata M, Yoshida H. Prevention and treatment of hepatocellular carcinoma. Liver Transpl 2004;10(Suppl):S111–4.

(13) Tsugane S, Gotlieb SL, Laurenti R, de Souza JM, Watanabe S. Cancer mortality among Japanese residents of the city of Sao Paulo, Brazil. Int J Cancer 1990;45:436–9.

(14) Tsugane S, Gotlieb SL, Laurenti R, Souza JM, Watanabe S. Mortality and cause of death among first-generation Japanese in Sao Paulo, Brazil. Int J Epidemiol 1989;18:647–51.

(15) Tsugane S, Sobue T. Baseline survey of JPHC study—design and participation rate. J Epidemiol 2001;11(6 Suppl):S24–9.

(16) World Health Organization. International classification of diseases for oncology. 3rd ed. Geneva (Switzerland): WHO; 2000.

(17) Stata Corporation. Stata statistical software, version 8.0. College Station (TX): Stata Corporation; 2003.

(18) Hasegawa R, Ogiso T, Imaida K, Shirai T, Ito N. Analysis of the potential carcinogenicity of coffee and its related compounds in a medium-term liver bioassay of rats. Food Chem Toxic 1995;33:15–20.

(19) Richelle M, Tavazzi I, Offord E. Comparison of the antioxidant activity of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. J Agric Food Chem 2001;49:3438–42.

(20) Gallus S, Tavani A, Negri E, La Vecchia C. Does coffee protect against liver cirrhosis? Ann Epidemiol 2002;12:202–5.

(21) Klatsky AL, Armstrong MA. Alcohol, smoking, coffee and cirrhosis. Am J Epidemiol 1992;136:1248–57.

(22) Tverdal A, Skurtveit D. Coffee intake and mortality from liver cirrhosis. Ann Epidemiol 2003;13:419–23.

(23) La Vecchia C, Negri E, Cavalieri d'Oro L, Franceschi S. Liver cirrhosis and the risk of primary liver cancer. Eur J Cancer Prev 1998;7:315–20.

(24) Tanaka K, Tokunaga S, Kono S, Tokudome S, Akamatsu T, Moriyama T, Zakouji H. Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers. Int J Epidemiol 1998;27:438–43.

(25) Honjo S, Kono S, Coleman MP, Shinchi K, Sakurai Y, Todoroki I, Umeda T, Wakabayashi K, Imanishi K, Nishikawa H, Ogawa S, Katsurada M, Nakagawa K, Yoshizawa N. Coffee consumption and serum aminotransferases in middle-aged Japanese men. J Clin Epidemiol 2001;54:823–9.

(26) Poikolainen K, Vartiainen E. Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. Am J Epidemiol 1997;146:1019–24.
(27) Wahllander A, Renner E, Preisig R. Fasting plasma caffeine concentration. A guide to the severity of chronic liver disease. Scand J Gastroenterol 1985;20:1133–41.
(28) Fukushima W, Tanaka T, Ofuji S, Hirota Y. Dietary habits and the risk of hepatocellular carcinoma among subjects with hepatitis C virus associated liver diseases. J Epidemiol 2004;14(1 Suppl):S47.
(29) Szabo E, Paska C, Kaposi Novak P, Schaff Z, Kiss A. Similarities and differences in hepatitis B and C virus induced hepatocarcinogenesis. Pathol Oncol Res 2004;10:5–11.

Notes

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Dietary patterns and subsequent colorectal cancer risk by subsite: A prospective cohort study

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In order to investigate the associations between dietary patterns and the risk of colorectal cancer by subsite in Japan, the baseline data from a population-based cohort study of 20,300 men and 21,812 women were analyzed. We conducted factor analysis and identified 3 major dietary patterns, "healthy," "traditional" and "Western," and calculated the factor scores of each pattern for individuals. During 10 years of follow-up, 370 colorectal cancer cases were identified. We found a positive association between the traditional pattern and colon cancer risk in women [rate ratio for highest quartile (RR) = 2.06; 95% CI = 1.10–3.84; *p* for trend = 0.11], but not in men. This positive association was slightly stronger for proximal colon cancer (RR = 2.07; 95% CI = 0.84–5.12) than for distal colon cancer (RR = 1.84; 95% CI = 0.75–4.50). After multivariate adjustment, the Western dietary pattern was also positively associated with colon cancer risk in females (RR = 2.21; 95% CI = 1.10–4.45), with the strongest associations being observed for females with distal colon cancer (RR = 3.48; 95% CI = 1.25–9.65). We did not observe any significant association between the healthy dietary pattern and colon cancer risk. For rectal cancer, no significant associations were found for the 3 dietary patterns. In conclusion, we found that the traditional and the Western dietary patterns were positively associated with colon cancer risk in females.

Key words: dietary pattern; colorectal cancer; subsite; Japan

Initial evidence from migrant and ecologic studies suggested that variations in colorectal cancer (CRC) incidence rates over time and between highly Westernized and less Westernized countries may be explained largely by changes or differences in environment factors, mainly dietary factors.[1–5] A number of previous epidemiologic evidences have indicated that individual foods or nutrients,[6–12] such as vegetables, fruits, fiber, animal fats, red meats, calcium, vitamin D, folate and Japanese traditional salty foods,[13] are possibly associated with the risk of colorectal cancer, but the results to date have not been completely consistent. Most previous epidemiologic studies have focused on individual nutrients and/or food. Only a few studies[14–16] have evaluated the relation of overall dietary pattern to the risk of CRC. A dietary pattern approach may provide additional insights that take into account the combined effects of foods. People eat meals consisting of a variety of foods with complex combinations of nutrients, not isolated nutrients. Because of the complexity of diets, the traditional approach with a single nutrient may potentially be confounded by the interactions between food components that are likely to be interactive or synergistic.[17] The overall dietary pattern that reflects many simultaneous dietary exposures may be an important complementary approach for elucidating relationships between diet and health.

Colorectal cancer incidence rates among Japanese were relatively lower than those among other developed countries, but the mortality and incidence rates of colorectal cancer have been gradually increasing in recent years.[18] These chronologic variations of CRC incidence and mortality rates in Japan could be associated with the change in dietary habits such as Westernization of diet [increase of animal foods (meat) consumption and decrease of grains simultaneously].[19]

The difference in incidence of CRC by subsite and gender has been determined in previous studies,[10,20–23] which indicate that there are different risk factors associated with proximal (right) and distal (left) colon carcinogenesis and with gender. Accordingly, using factor analysis in the present investigation, we identified the dietary patterns and evaluated the associations between dietary patterns and colon and rectal cancer risks in a population-based cohort study, the Japan Public Health Center (JPHC)-based prospective study on cancer and cardiovascular diseases (JPHC Study Cohort I).

Material and methods

Study cohort

The JPHC Study Cohort I is a population-based prospective study launched in 1990. The study cohort included 54,498 residents (27,063 men and 27,435 women) from 14 administrative districts supervised by 4 public health centers (PHCs): Ninohe PHC area of Iwate Prefecture, Yokote PHC area of Akita, Saku PHC areas of Nagano and Ishikawa PHC area of Okinawa. Study population was defined to be all inhabitants in the study areas aged 40–59 years at the beginning of the study (1 January 1990). The study design has been described in detail previously.[24] The JPHC study was approved by the institutional review board at the National Cancer Center.

Baseline questionnaire

The self-administered food-frequency questionnaire (FFQ) includes 44 food groups that were commonly consumed in this study population. Participants indicated their average frequency of consumption for each food group over the past month. For rice, inquiry was made as to the number of bowls consumed per day. The frequency of miso (fermented soybean paste) soup consumption was classified into 4 categories: rarely (< 1 day/week), 1–2 days/week, 3–4 days/week and almost every day (6 or more days/week), and the number of bowls per day was asked in the same manner as for rice intake. The frequency of other food group items was classified into 4 categories: rarely (< 1 day/week), 1–2 days/week, 3–4 days/week and almost every day (6 or more days/week). For each of the 9 nonalcoholic beverage items (green tea, Chinese tea, black tea, other teas, coffee, milk, soda, fruit juice, vegetable juice), the intake frequency was asked using 6 categories: rarely (< 1 day/week), 1–2 days/week, 3–4 days/week, 1–2 cups/day, 3–4 cups/day and 5 or more cups/day. Questions on the consumption frequency of 5 alcoholic beverages (sake,

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shochu, beer, whiskey and other) covered 6 categories (almost never, 1–3 days per month, 1–2 days per week, 3–4 days per week, 5–6 days per week, almost every day). The selected frequency category for each item was converted to a weekly intake. In calculating the amount of each food item and nutrients, we used the serving size based on the observed median values from the 14–28 day diet record data.[25] Nutrients values were adjusted for total energy intake using the residual method.[26] The diet record data were also used to assess the validity of the questionnaire. The validity and reproducibility of the FFQ used in this study were reported previously.[27]

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

Follow-up and identification of cancer cases

We followed all registered cohort subjects from 1 January 1990 to 31 December 1999. Incident cases of cancer occurring in the cohort have been identified through continuous surveillance of hospital records, population-based cancer registries and death certificates. This detailed follow-up procedure was described elsewhere.[24] Cases of colorectal cancer were extracted from the JPHC cancer registry based on site codes [International Classification of Diseases for Oncology, 2nd edition (ICD-O-2) code: C180-C189 (colon) and C199, C209 (rectum)]. A total of 370 cases of colorectal cancer (231 males and 139 females) were documented with pathologically confirmed diagnoses such as adenocarcinoma, including adenocarcinoma *in situ*, occurring in 1990–1999 as of November 2000. For analyses of colon cancer by anatomic subsite, proximal colon cancers were defined as those occurring from the cecum up through the splenic flexure ($n = 112$). Distal colon cancers were defined as those occurring from the descending colon up through the sigmoid colon ($n = 122$). The location of colon cancers was not specified ($n = 14$).

Assessment of dietary patterns

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

Statistical analysis

A Cox's proportional-hazards model was used to calculated the relative risks (RRs) for each quartile compared with the lowest quartile of each dietary pattern score using PROC PHREG of the SAS program (SAS Institute). In these analyses, age, body mass index, total energy intake, education level, physical activity and family histories of colorectal cancer were used as covariates. Smoking habit and alcohol consumption were further added in the multivariate models only for men. We tested for linear trends across categories of dietary patterns by assigning each participant the median value for the category and modeling this value as a continuous variable. All analyses were separately conducted for men and women. For colon cancer, subgroup analyses were performed for proximal and distal colon cancer. In a separate analysis, we also conducted analysis jointly classifying subjects by major dietary pattern and age (≥ 50), obesity status (body mass index ≥ 25) and smoking status. PHC areas were also added in the multivariate models only for the "healthy" and the "Western" dietary patterns, not for the "traditional" dietary pattern, because the associations with salted food intake were always attenuated after adjusting for PHC area, where intakes varied significantly between areas.

Results

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

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

The relative risks (RR) and 95% confidence intervals (CIs) of each quartile of dietary patterns are shown in Table IV. After adjustment for the potential confounders, a higher traditional dietary pattern score was significantly associated with increased risk of colon cancer in females, but not in males. The multivariate-

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

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

Absolute values < 0.15 were not listed for simplicity.

adjusted RR for the highest quartile of the traditional dietary pattern score in female was 2.06 (95% CI = 1.10–3.84) comparing with the lowest, though the test for linear trend was not significant. There was no substantial difference in this positive association between proximal colon cancer (RR = 2.07; 95% CI = 0.84–5.12) and distal cancer (RR = 1.84; 95% CI = 0.75–4.50). No significant associations were observed between the traditional dietary pattern and rectal cancer in either gender, although a higher traditional dietary pattern score was suggested to decrease the risk of rectal cancer in male (RR = 0.62; 95% CI = 0.28–1.39).

After multivariate adjustment, the Western dietary pattern was also positively associated with the risk of colon cancer but only in females. The multivariate-adjusted RR for the highest quartile of the Western dietary pattern score in female was 2.21 (95% CI = 1.10–4.45) comparing with the lowest, although the test for linear trend was not significant. When the upper 3 quartiles were combined and compared to the lowest quintile, the Western dietary pattern was associated with a significantly higher risk (RR = 1.98, 95% CI = 1.11–3.52 in colon cancer; RR = 2.43, 95% CI = 1.01–5.91 in distal colon cancer; results not shown). The positive association was slightly stronger for distal colon cancer (RR = 3.48; 95% CI = 1.25–9.65) than for proximal cancer (RR = 1.66; 95% CI = 0.60–4.64). Fiber intakes (total, water-soluble, and water-insoluble) have been reported to be inversely associated with the risk of colorectal cancer.[28] To examine whether the positive association for the Western dietary pattern was mediated by these nutrients, we included fiber intakes in the multivariate model. Further adjustment for fiber intakes did not alter this positive association for the Western dietary pattern score of females substantially: the RR for the comparison of the highest with the lowest quartile was 3.60 (95% CI = 1.29–10.1) in distal colon. No significant association was observed between the Western dietary pattern and rectal cancer in either gender.

Evaluation of dietary patterns with regard to risk of colon and rectal cancers showed that no apparent associations were found between the healthy dietary pattern and colorectal cancer risk, although nonsignificant inverse associations were suggested to exist in proximal colon cancer. The multivariate-adjusted RRs for the highest *versus* the lowest quartile of the healthy dietary pattern score in proximal colon cancer were 0.47 (95% CI = 0.18–1.23) in females and 0.68 (95% CI = 0.32–1.47) in males.

In a subgroup analyses stratified by known risk factors, the associations between the 3 dietary patterns and risk of colon and rectal cancers were generally consistent across different strata according to smoking status, body mass index and age. However, the associations with the Western dietary pattern in distal colon cancer were slightly stronger among male smokers and among females below age 50 years. For distal colon cancer, the multivari-

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

	Dietary pattern	Quartile of dietary pattern score			
		1 (lowest)	2	3	4 (highest)
Age (years)	Healthy	48.0 ± 5.8[1]	49.2 ± 5.9	49.9 ± 5.9	50.7 ± 5.9
	Traditional	49.0 ± 5.9	49.1 ± 5.9	49.4 ± 6.0	50.3 ± 5.8
	Western	50.7 ± 5.8	49.5 ± 5.9	49.0 ± 6.0	48.7 ± 5.9
Body mass index (kg/m^2)	Healthy	24 ± 3	24 ± 3	23 ± 3	23 ± 3
	Traditional	24 ± 3	23 ± 3	23 ± 3	23 ± 3
	Western	23 ± 3	24 ± 3	24 ± 3	24 ± 3
Education (college or higher) (%)	Healthy	12.6	13.9	14.8	15.8
	Traditional	18.6	17.0	12.9	8.5
	Western	13.1	14.6	14.6	14.8
Leisure-time physical activity (≥ 1 time/week; %)	Healthy	15.2	16.1	18.0	20.8
	Traditional	21.2	19.4	16.1	13.3
	Western	13.6	16.9	18.3	21.3
Current smoker (%)	Healthy	60.8	54.9	51.8	45.1
	Traditional	44.4	50.9	57.2	60.2
	Western	48.9	53.9	53.7	56.3
Drinker (≥ 5 times/week; %)	Healthy	51.9	50.6	48.7	43.1
	Traditional	15.5	36.6	61.0	81.0
	Western	40.7	48.5	51.7	53.4
Family history of colorectal cancer (%)	Healthy	0.83	1.04	0.87	1.10
	Traditional	0.79	1.10	1.08	0.87
	Western	1.34	0.97	0.81	0.73
Total energy (kcal)[2]	Healthy	1,817	2,037	2,153	2,323
	Traditional	1,641	1,957	2,249	2,584
	Western	2,116	2,040	2,002	2,173
Nutrient intakes (energy-adjusted)[2,3]					
Carbohydrates (g)	Healthy	316	318	316	312
	Traditional	325	322	313	302
	Western	337	320	308	294
Fiber (g)	Healthy	6.13	7.66	8.81	10.45
	Traditional	7.89	8.28	8.39	8.38
	Western	8.72	8.15	7.98	8.12
Protein (g)	Healthy	52.0	58.1	62.3	68.2
	Traditional	58.9	59.8	60.1	61.8
	Western	58.5	59.2	60.0	63.2
Fat (g)	Healthy	23.5	27.5	30.9	35.7
	Traditional	32.0	29.4	28.3	27.7
	Western	25.2	27.5	29.9	34.7
Alcohol (g)	Healthy	52.8	40.7	34.9	28.1
	Traditional	34.0	37.4	37.8	40.8
	Western	34.9	38.6	40.1	39.9
Sodium (mg)	Healthy	1,797	2,104	2,250	2,333
	Traditional	1,702	2,038	2,255	2,450
	Western	2,143	2,091	2,094	2,279
Vitamin A (IU)	Healthy	1,155	1,775	2,674	4,493
	Traditional	2,204	2,003	2,124	4,354
	Western	1,384	1,798	4,449	5,358
Carotenoid (mg)	Healthy	898	1,210	1,704	2,299
	Traditional	1,635	1,527	1,448	1,488
	Western	1,409	1,373	1,519	1,705
Vitamin C (mg)	Healthy	42.3	58.6	71.5	89.8
	Traditional	59.8	64.2	67.3	69.8
	Western	65.5	62.4	63.9	70.9

[1]Mean ± SD. –[2]Median. –[3]Energy-adjusted nutrient intake by residual method.

ate adjusted RRs for the highest quartile of the Western dietary pattern compared with the lowest were 2.58 (95% CI = 0.93–7.18) in male smokers and 4.17 (95% CI = 1.05–16.6) in younger females (results not shown).

Discussion

The relationship between dietary pattern and the risk of colon and rectal cancer was examined in a population-based prospective study of 42,112 Japanese in the JPHC study. We identified the 3 distinct dietary patterns, healthy, traditional and Western, in this population and found that the traditional and Western dietary patterns were positively associated with colon cancer risk in female, independent of other lifestyle variables, whereas the healthy dietary pattern was not associated with risk. The positive association between the traditional dietary pattern and colon cancer risk was more prominent among women with proximal colon cancer, while the positive association between the Western dietary pattern and colon cancer risk was more prominent among women with distal colon cancer.

For the last 5 decades, the incidence and mortality rates of colorectal cancer have been sharply increasing in Japan, especially those due to distal colon cancer in the urbanized areas rather than in rural areas, but those due to proximal colon cancer have been mostly stable.[29,30] Furthermore, proximal colon cancer in females was more prevalent in rural areas than in urban areas, where distal colon cancer was prominent.[30] Secular changes and geographic variations of the incidence and mortality rates due to colon cancer by subsite may imply that the risk factors for right-sided (proximal) colon cancer may differ from those for left-sided (distal)

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

	Dietary pattern	Quartile of dietary pattern score			
		1 (lowest)	2	3	4 (highest)
Age (years)	Healthy	48.9 ± 5.9[1]	49.4 ± 5.8	49.7 ± 5.8	50.4 ± 5.9
	Traditional	48.6 ± 5.9	49.1 ± 5.9	49.8 ± 5.9	50.9 ± 5.5
	Western	50.9 ± 5.7	49.7 ± 5.8	49.1 ± 5.9	48.8 ± 5.8
Body mass index (kg/m^2)	Healthy	24 ± 3	24 ± 3	23 ± 3	23 ± 3
	Traditional	24 ± 4	23 ± 3	23 ± 3	24 ± 3
	Western	24 ± 3	24 ± 3	24 ± 3	24 ± 3
Education (college or higher) (%)	Healthy	9.8	10.7	12.1	15.6
	Traditional	16.5	14.0	10.4	7.3
	Western	11.9	11.8	12.3	12.3
Leisure-time physical activity (≥ 1 time/week; %)	Healthy	9.32	12.1	15.7	20.9
	Traditional	16.8	16.5	13.9	10.8
	Western	14.5	13.8	14.0	15.7
Current smoker (%)	Healthy	9.1	5.0	4.9	3.8
	Traditional	7.4	6.4	4.9	4.0
	Western	3.9	5.4	6.1	7.4
Drinker (≥ 5 times/week)	Healthy	5.2	3.4	3.4	3.3
	Traditional	2.6	4.4	4.1	4.2
	Western	2.9	3.3	4.1	5.1
Family history of colorectal cancer (%)	Healthy	0.73	0.86	1.03	1.14
	Traditional	0.57	1.32	1.03	0.84
	Western	0.79	1.14	0.94	0.90
Total energy (kcal)[2]	Healthy	1,175	1,309	1,394	1,525
	Traditional	1,208	1,337	1,405	1,518
	Western	1,256	1,309	1,367	1,544
Nutrient intakes (energy-adjusted)[2,3]					
Carbohydrates (g)	Healthy	223	213	207	200
	Traditional	206	209	211	214
	Western	218	212	208	202
Fiber (g)	Healthy	7.4	9.2	10.4	11.9
	Traditional	8.8	9.8	10.2	10.3
	Western	10.3	9.8	9.6	9.8
Protein (g)	Healthy	46.7	52.0	55.3	59.3
	Traditional	50.8	52.7	54.2	56.7
	Western	51.5	52.4	53.6	56.8
Fat (g)	Healthy	25.8	30.8	33.8	38.4
	Traditional	34.1	32.9	32.0	30.7
	Western	27.8	30.7	33.0	37.5
Alcohol (g)	Healthy	10.8	6.4	5.1	4.0
	Traditional	8.6	6.1	4.9	5.7
	Western	6.3	6.7	6.6	5.7
Sodium (mg)	Healthy	2,002	2,195	2,279	2,279
	Traditional	1,623	2,051	2,370	2,650
	Western	2,179	2,153	2,160	2,379
Vitamin A (IU)	Healthy	1,605	2,250	2,868	3,523
	Traditional	3,502	2,824	2,625	2,432
	Western	2,225	2,399	3,179	6,680
Carotenoid (mg)	Healthy	1,497	2,352	2,752	4,239
	Traditional	2,537	2,592	2,573	2,519
	Western	2,597	2,492	2,498	2,648
Vitamin C (mg)	Healthy	74.2	99.3	117.5	138.5
	Traditional	91.9	109.3	114.9	118.5
	Western	108.3	104.4	106.3	117.8

[1]Mean ± SD. –[2]Median. –[3]Energy-adjusted nutrient intake by residual method.

colon cancer. It is noteworthy that there may be different risk factors in the etiology of right colon cancer in rural areas and left colon cancer in urbanized areas in Japan. The rapid rise in CRC incidence parallels the changes in eating habits and Westernization of lifestyle among Japanese.[19] Dietary changes over the last several decades, especially reduced intake of carbohydrates and salted foods, increased intake of fats and animal foods, as well as Westernized dietary practice, were considered the major plausible explanations for increasing trends in colorectal cancer in Japan.[18,19] The present result also suggested that the recent Westernization of eating habits of Japanese might be associated with the recent increase in mortality rates for distal colon cancer in Japan. From the present findings, it was suggested that the association of the Western dietary pattern with distal colon cancer was more apparent especially among females below age 50 and may reflect the change to Westernized eating habits, despite the small number of cancers in this subgroup analysis. Thus, interpretations should be made cautiously. Furthermore, it is important to note that we cannot always explain the time trend of disease by a single factor, and the findings from ecologic and cohort studies are sometimes inconsistent. Also, the results should be verified in a larger prospective study.

Direct comparison between the present and previous findings from the individual nutrient/food approach is difficult. Because there are many potential differences in nutrients between dietary patterns, this approach cannot be specific about the particular nutrients responsible for the observed differences in disease risk and thus it may not be very informative about any biologic rela-

TABLE IV – MULTIVARIATE RELATIVE RISKS OF COLORECTAL CANCER WITH 95% CONFIDENCE INTERVALS ACCORDING TO QUARTILE OF THE 3 MAJOR DIETARY PATTERNS: JPHC STUDY 1990–1999

	Quartiles (male)				*p* for trend	Quartiles (female)				*p* for trend
	1 (low)	2	3	4 (high)		1 (low)	2	3	4 (high)	
Healthy dietary pattern										
Person-years	47,265	47,481	47,622	47,710		52,124	52,338	52,530	52,289	
Colorectal cancer										
Cases	60	57	61	53		37	37	29	36	
Multivariate[1]	1.00	0.88 (0.60–1.30)	1.01 (0.69–1.48)	0.81 (0.52–1.24)	0.80	1.00	0.94 (0.58–1.51)	0.80 (0.48–1.32)	0.98 (0.58–1.65)	0.82
Colon cancer										
Cases	37	39	44	36		24	23	25	20	
Multivariate	1.00	0.97 (0.60–1.54)	1.13 (0.71–1.80)	0.83 (0.49–1.41)	0.62	1.00	0.88 (0.48–1.60)	1.02 (0.57–1.85)	0.76 (0.39–1.50)	0.68
Proximal colon										
Cases	16	15	19	17		15	9	11	10	
Multivariate	1.00	0.73 (0.35–1.52)	0.90 (0.45–1.82)	0.68 (0.32–1.47)	0.83	1.00	0.45 (0.18–1.13)	0.67 (0.29–1.52)	0.47 (0.18–1.23)	0.96
Distal colon										
Cases	18	21	21	19		8	14	11	10	
Multivariate	1.00	1.18 (0.61–2.29)	1.36 (0.69–2.68)	1.10 (0.52–2.36)	0.93	1.00	1.84 (0.76–4.45)	1.48 (0.57–3.82)	1.50 (0.53–4.21)	0.62
Rectal cancer										
Cases	23	18	17	17		13	14	4	16	
Multivariate	1.00	0.74 (0.38–1.43)	0.79 (0.40–1.54)	0.76 (0.37–1.58)	0.76	1.00	1.05 (0.48–2.30)	0.33 (0.11–1.05)	1.43 (0.62–3.28)	0.34
Traditional dietary pattern										
Person-years	46,883	47,043	47,711	48,441		51,611	52,011	52,487	53,172	
Colorectal cancer										
Cases	48	51	59	73		31	32	29	47	
Multivariate	1.00	0.89 (0.58–1.36)	0.91 (0.58–1.42)	0.88 (0.55–1.42)	0.70	1.00	1.06 (0.64–1.76)	0.96 (0.57–1.63)	1.53 (0.93–2.52)	0.23
Colon cancer										
Cases	32	39	37	48		18	21	18	35	
Multivariate	1.00	1.06 (0.63–1.76)	1.01 (0.58–1.76)	1.05 (0.58–1.90)	0.68	1.00	1.20 (0.63–2.29)	1.04 (0.53–2.05)	2.06 (1.10–3.84)	0.11
Proximal colon										
Cases	12	18	15	22		8	10	7	20	
Multivariate	1.00	1.17 (0.53–2.56)	0.91 (0.39–2.16)	1.06 (0.44–2.55)	0.97	1.00	1.17 (0.45–3.07)	0.75 (0.25–2.20)	2.07 (0.84–5.12)	0.20
Distal colon										
Cases	17	17	21	24		10	11	9	13	
Multivariate	1.00	0.91 (0.43–1.92)	1.24 (0.58–2.63)	1.21 (0.53–2.77)	0.26	1.00	1.25 (0.53–2.99)	1.12 (0.44–2.84)	1.84 (0.75–4.50)	0.53
Rectal cancer										
Cases	16	12	22	25		13	11	11	12	
Multivariate	1.00	0.59 (0.28–1.29)	0.73 (0.35–1.54)	0.62 (0.28–1.39)	0.87	1.00	0.87 (0.39–1.97)	0.84 (0.37–1.94)	0.85 (0.36–2.02)	0.84
Western dietary pattern										
Person-years	47,649	47,862	47,309	47,258		52,618	52,302	52,274	52,086	
Colorectal cancer										
Cases	64	59	55	53		36	37	32	34	
Multivariate	1.00	0.98 (0.67–1.43)	0.96 (0.65–1.41)	0.93 (0.62–1.41)	0.85	1.00	1.31 (0.81–2.12)	1.22 (0.73–2.03)	1.45 (0.85–2.48)	0.59
Colon cancer										
Cases	39	43	39	35		19	27	22	24	
Multivariate	1.00	1.15 (0.72–1.82)	1.11 (0.69–1.79)	1.05 (0.63–1.75)	0.73	1.00	2.01 (1.07–3.81)	1.80 (0.92–3.52)	2.21 (1.10–4.45)	0.74
Proximal colon										
Cases	16	19	18	14		12	13	10	10	
Multivariate	1.00	1.37 (0.67–2.78)	1.37 (0.66–2.85)	1.17 (0.53–2.56)	0.61	1.00	1.89 (0.78–4.61)	1.62 (0.62–4.20)	1.66 (0.60–4.64)	0.87
Distal colon										
Cases	20	22	17	20		6	12	11	14	
Multivariate	1.00	1.04 (0.55–1.98)	0.89 (0.44–1.77)	1.10 (0.55–2.20)	0.84	1.00	2.15 (0.80–5.77)	2.18 (0.79–6.03)	3.48 (1.25–9.65)	0.30
Rectal cancer										
Cases	25	16	16	18		17	10	10	10	
Multivariate	1.00	0.71 (0.37–1.37)	0.70 (0.36–1.39)	0.73 (0.36–1.46)	0.87	1.00	0.66 (0.30–1.46)	0.68 (0.30–1.55)	0.77 (0.32–1.83)	0.64

[1]Multivariate adjustment included age, body mass index, study area (for the healthy and Western dietary pattern), energy intake, education level, physical activity, family history of colorectal cancer, smoking status (for males) and alcohol consumption (for males).

tionship between dietary components and disease risk. Nevertheless, our findings are consistent with the previous findings of associations of single nutrients and foods identified in earlier studies, in which higher consumption of red meat,[6] especially heterocyclic amines (HCAs),[9] fat,[6,11] carbohydrates[23] and salty foods[13] has been associated with an increased risk of colorectal cancer. Furthermore, the dietary pattern approach is basically population-based, and if some foods were added or excluded, dietary patterns may be slightly changed. Thus, direct comparison even between the findings with dietary pattern analysis is difficult. Therefore, the results from the dietary pattern analysis should be interpreted carefully. Nevertheless, the dietary patterns identified in the present study were similar to those from previous studies among Japanese and Western populations. Interestingly, these 2 patterns, *i.e.*, healthy and Western, were qualitatively similar to those of the Western population. The healthy pattern in the present study was also similar to the "healthy,"[31] "vegetable and fruit"[32] and "prudent"[14,16,33] patterns identified in other studies. The Western pattern in our study was similar to those labeled "Western,"[34] "Western breakfast" and "meat"[32] among the Japanese population and the "Western" pattern among the U.S.[14,16] and Swedish[33] populations. However, the traditional pattern was, as expected, the distinctive dietary pattern for Japanese, which included traditional staple foods, rice and many kinds of salted foods, such as pickled vegetables and salted fish and roe, which may be an indirect marker of genotoxic carcinogen exposure. The traditional pattern in the present study was similar to the "rice/snack" pattern identified among Japanese.[32] In our previous report,[35] the healthy and the traditional dietary patterns were significantly associated with the risk of gastric cancer. In fact, a similarity in the geographic distribution of colorectal and gastric cancers was identified in Japan. The correlation coefficients of age-adjusted mortality rate of colorectal and gastric cancer within 47 prefectures of Japan in 1995 were 0.43 in men and 0.33 in women (unpublished data).

To the best of our knowledge, only 3 previous epidemiologic studies have examined the associations between dietary pattern and CRC risk. In a case-control study in the of United States[14] and a prospective study of U.S. women,[16] the risk of colon cancer was positively associated with the Western dietary pattern and negatively associated with a "prudent" pattern. Even though our study population and their dietary characteristics were different from the previous findings in the U.S. population, the positive association between the Western dietary pattern and colon cancer risk is consistent with what was observed in previous studies of the Western dietary pattern. However, in a prospective study of Swedish women,[15] there was no clear association between a Western, healthy, or drinker dietary pattern and CRC risk. However, these 2 previous cohort studies were limited only to women subjects. Although the healthy dietary pattern has been hypothesized to be associated with lower risk of colorectal cancer through the dietary antioxidant effects of β-carotene, vitamin C and vitamin E,[8] it was not significantly associated with the risk of CRC in the present study.

This observed result gives support to a unifying hypothesis that diet and associated factors, such as physical activity and body size, increase the risk of colorectal cancer via their effects on serum insulin concentrations and on the bioavailability of insulin-like growth factor-I.[36,37] As for the most important among the environmental factors influencing the CRC risk, diets that are high in meat, saturated fats, refined carbohydrates and processed foods and low in vegetables, fruits and fiber have nearly all been associated with an increased risk of CRC.[9,23,37] Diets high in carbohydrate, especially the digestible nonfiber portion of carbohydrates, may lead to a chronic state of elevated insulin and stimulate growth of colorectal tumors,[23] although an excessive carbohydrate intake might not be linked with hyperinsulinemia in a healthy young subject. In addition, high carbohydrate consumption is closely linked to salty food consumption in Japan, as shown in the present study. A high consumption of salted fish, shellfish and vegetables has been reported to be associated with the increased risk of CRC.[13,38,39] The mechanism, however, is unclear, and there is no evidence that nitrosamines contained in salt-preserved foods are involved in the development of colon cancer in humans. Nevertheless, N-nitrosamine has shown mutagenicity and carcinogenicity in laboratory animals.[38]

In the present study, we could not obtain consistent findings for dietary risk factors between male and female, although they were claimed to be risk or protective factors in Western populations. Given the male-female differences in incidence by subsite,[22] it is likely that one or more risk factors might also exhibit differences such as those observed in this study. It was reported in a previous study[40] that response to the dietary questionnaire might be more precise and reliable in females than in males, because females in Japan generally prepare the meals and are more conscious of diet and foods. However, in our previous study, there was no gender difference in the validity of a self-administered food frequency questionnaire in comparison with 28- or 14-day dietary records.[25] The differential associations with the dietary pattern in men and women may be partially explained by the fact that other lifestyle factors, such as percentage of smokers and habitual drinkers, were substantially different within each dietary pattern between genders. The role of cigarette smoking and alcohol drinking may be strongly associated with the risk among men.[41]

The observed site-specific differences in risk between the genders, however, suggest possible differences in etiology for proximal and distal colon cancers that are consistent with women's higher incidence of proximal colon tumors and adenomas.[22,42] Distinct epidemiologic and clinicopathologic characteristics of CRCs based on their anatomical location suggest different risk factors and pathways of transformation associated with proximal and distal colon carcinogenesis. These differences may reflect distinct biologic characteristics of proximal and distal colonic mucosa, acquired in embryonic or postnatal development, that determine a differential response to uniformly distributed environmental factors.[20]

It is important to note that dietary patterns are associated with health behaviors, lifestyle and sociodemographic factors.[43,44] As shown in Tables II and III, major dietary patterns were associated with demographic factors and lifestyle habits. Therefore, we cannot exclude the possibility that not only dietary factors defined as dietary patterns, but also their related demographic and lifestyle factors, may affect the CRC risk, even though the related lifestyle variables were considered as potential confounders in the multivariate model.

This cohort study has been conducted in a large sample of men and women from the general Japanese population. One of its strengths is the high rate of participation and the completeness of follow-up, indicating that selection bias due to loss of follow-up is highly unlikely. Another strength of the prospective design is that the diet was measured before the disease was diagnosed, which diminishes the probability of recall bias of dietary intake. We have also controlled extensively for potential confounders. However, it is likely that unmeasured or unidentified risk factors may have affected the study results.

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

In conclusion, the major dietary patterns of Japanese were identified using factor analysis, and the present findings indicated that the traditional and the Western dietary pattern were positively associated with colon cancer risk in females.

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References

1. Haenszel W, Kurihara M. Studies of Japanese migrants: I, mortality from cancer and other diseases among Japanese in the United States. J Natl Cancer Inst 1968;40:43–6.
2. Haenszel W, Berg JW, Segi M, Kurihara M, Locke FB. Large-bowel cancer in Hawaiian Japanese. J Natl Cancer Inst 1973;51:1765–79.
3. IARC.Cancer incidence in five continents, vol 4. Lyon: IARC, 1982.
4. Potter JD. Nutrition and colorectal cancer. Cancer Causes Control 1996;7:127–46.
5. Whittemore AS, Wu-Williams AH, Lee M, Shu Z, Gallagher RP, Deng-ao J, Lun Z, Xianghui W, Kun C, Jung D, Teh CZ, Chengde L, *et al.* Diet, physical activity, and colorectal cancer among Chinese in North America and China. J Natl Cancer Inst 1990;82:915–26.
6. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990;323:1664–72.
7. Marcus PM, Newcomb PA. The association of calcium and vitamin D, and colon and rectal cancer in Wisconsin women. Int J Epidemiol 1998;27:788–93.
8. Satia-Abouta J, Galanko JA, Martin CF, Potter JD, Ammerman A, Sandler RS. Associations of micronutrients with colon cancer risk in African Americans and Whites: results from the North Carolina Colon Cancer Study. Cancer Epidemiol Biomarkers Prev 2003;12:747–54.
9. Butler LM, Sinha R, Millikan RC, Martin CF, Newman B, Gammon MD, Ammerman AS, Sandler RS. Heterocyclic amines, meat intake, and association with colon cancer in a population-based study. Am J Epidemiol 2003;157:434–45.
10. Voorrips LE, Goldbohm RA, van Poppel G, Sturmans F, Hermus RJJ, van den Brandt PA. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: the Netherlands cohort study on diet and cancer. Am J Epidemiol 2000;152:1081–92.
11. McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. J Natl Cancer Inst 1985;75:185–91.
12. Terry P, Jain M, Miller AB, Howe GR, Rohan TE. Dietary intake of folic acid and colorectal cancer risk in a cohort of women. Int J Cancer 2002;97:864–7.
13. Tajima K, Tominaga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. Jpn J Cancer Res 1985;76:705–16.
14. Slattery ML, Boucher KM, Caan BJ, Potter JD, Ma KN. Eating patterns and risk of colon cancer. Am J Epidemiol 1998;148:4–16.
15. Terry P, Hu FB, Hansen H, Wolk A. Prospective study of major dietary patterns and colorectal cancer risk in women. Am J Epidemiol 2001;154:1143–9.
16. Fung T, Hu FB, Fuchs C, Giovannucci E, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC. Major dietary patterns and the risk of colorectal cancer in women. Arch Intern Med 2003;163:309–14.
17. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 2002;13:3–9.
18. Ministry of Health, Labor and Welfare. Vital statistics of Japan. Tokyo: Ministry of Health, Labor and Welfare, 2003.
19. Ministry of Health, Labor and Welfare. The national nutrition survey in Japan, 2000. Tokyo: Daiichi Shuppan Publishers, 2002.
20. Glebov OK, Rodriguez LM, Nakahara K, Jenkins J, Cliatt J, Humbyrd CJ, DeNobile J, Soballe P, Simon R, Wright G, Lynch P, Patterson S, *et al.* Distinguishing right from left colon by the pattern of gene expression. Cancer Epidemiol Biomarkers Prev 2003;12:755–62.
21. Toyomura K, Yamaguchi K, Kawamoto H, Tabata S, Shimizu E, Mineshita M, Ogawa S, Lee KY, Kono S. Relation of cigarette smoking and alcohol use to colorectal adenomas by subsite: the Self-Defense Forces Health Study. Cancer Sci 2004;95:72–6.
22. McCashland TM, Brand R, Lyden E, de Garmo P, CORI Research Project. Gender differences in colorectal polyps and tumors. Am J Gastroenterol 2001;96:882–6.
23. Borugian MJ, Sheps SB, Whittemore AS, Wu AH, Potter JD, Gallagher RP. Carbohydrates and colorectal cancer risk among Chinese in North America. Cancer Epidemiol Biomarkers Prev 2002;11:187–93.
24. Tsugane S, Fahey M, Sasaki S, Baba S. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC Study Cohort I. Am J Epidemiol 1999;150:1201–7.
25. Tsubono Y, Sasaki S, Kobayashi M, Akabane M, Tsugane S. Food composition and empirical weight methods in predicting nutrient intakes from food frequency questionnaire. Ann Epidemiol 2003;11:213–8.
26. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
27. Tsubono Y, Kobayashi M, Sasaki S, Tsugane S. Validity and reproducibility of a self-administered food frequency questionnaire used in the baseline survey of the JPHC Study Cohort I. J Epidemiol 2003;13:S125–33.
28. Howe GR, Benito E, Castelleto R, Cornee J, Esteve J, Gallagher RP, Iscovich JM, Deng-ao J, Kaaks R, Kune GA, Kune S, L'Abbe KA, *et al.* Dietary intake of fiber and decreased risk of cancers of the colon and rectum: evidence from the combined analysis of 13 case-control studies. J Natl Cancer Inst 1992;84:1887–96.
29. Research Group for Population-based Cancer Registration in Japan. Cancer incidence and incidence rates in Japan in 1997: estimates based on data from 12 population-based cancer registries. Jpn J Clin Oncol 2002;32:318–22.
30. Tajima K, Hirose K, Nakagawa N, Kuroishi T, Tominaga S. Urban-rural difference in the trend of colorectal cancer mortality with special reference to the subsites of colon cancer in Japan. Jpn J Cancer Res 1985;76:717–28.
31. Chen H, Ward MH, Graubard BI, Heineman EF, Markin RM, Potischman NA, Russell RM, Weisenburger DD, Tucker KL. Dietary patterns and adenocarcinoma of the esophagus and distal stomach. Am J Clin Nutr 2002;75:137–44.
32. Masaki M, Sugimori H, Nakamura K, Tadera M. Dietary patterns and stomach cancer among middle-aged male workers in Tokyo. Asian Pac J Cancer Prev 2003;4:61–6.
33. Terry P, Suzuki R, Hu FB, Wolk A. A prospective study of major dietary patterns and the risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2001;10:1281–5.
34. Nakamura M, Whitlock G, Aoki N, Nakashima T, Hoshino T, Yokoyama T, Morioka S, Kawamura T, Tanaka H, Hashimoto T, Ohno Y. Japanese and Western diet and risk of idiopathic sudden deafness: a case-control study using pooled controls. Int J Epidemiol 2001;30:608–15.
35. Kim MK, Sasaki S, Sasazuki S, Tsugane S. Prospective study of three major dietary patterns and risk of gastric cancer in Japan. Int J Cancer 2004;110:435–42.
36. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst 2002;94:972–80.
37. Giovannucci E. Insulin and colon cancer. Cancer Causes Control 1995;6:164–79.
38. Guo W, Zheng W, Li JY, Chen JS, Blot WJ. Correlations of colon cancer mortality with dietary factors, serum markers, and schistosomiasis in China. Nutr Cancer 1993;20:13–20.
39. Chiu BC, Ji BT, Dai Q, Gridley G, McLaughlin JK, Gao YT, Fraumeni JF Jr, Chow WH. Dietary factors and risk of colon cancer in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2003;12:201–8.
40. Shibata A, Paganini-Hill A, Ross RK, Henderson BE. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 1992;66:673–9.
41. Otani T, Iwasaki M, Yamamoto S, Sobue T, Hanaoka T, Inoue M, Tsugane S. Alcohol consumption, smoking, and subsequent risk of colorectal cancer in middle-aged and elderly Japanese men and women: Japan Public Health Center-based prospective study. Cancer Epidemiol Biomarkers Prev 2003;12:1492–500.
42. Potter JD, Slattery ML, Bostick RM, Gapstur SM. Colon cancer: a review of the epidemiology. Epidemiol Rev 1993;15:499–545.
43. Sanchez-Villegas A, Delgado-Rodriguez M, Martinez-Gonzalez MA, de Irala-Estevez J. Gender, age, socio-demographic and lifestyle factors associated with major dietary patterns in the Spanish Project SUN (Seguimiento Universidad de Navarra). Eur J Clin Nutr 2003;57:285–92.
44. Whichelow MJ, Prevost AT. Dietary patterns and their associations with demographic, lifestyle and health variables in a random sample of British adults. Br J Nutr 1996;76:17–30.

Appendix

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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.
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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.

TABLE IV – RELATIVE RISKS (RR) AND 95% CONFIDENCE INTERVALS (CI) OF LUNG CANCER RELATIVE TO MENOPAUSAL METHOD ACCORDING TO STATUS OF HORMONE USE AMONG MENOPAUSAL NEVER-SMOKING WOMEN[1]

Hormone use	Natural menopause	RR (95% CI)	Induced menopause	RR (95% CI)
Hormone use −				
Total cases	72		11	
Person-years	158,955	1.00	24,223	1.19 (0.61–2.30)
Hormone use +				
Total cases	11		7	
Person-years	21,442	1.19 (0.60–2.33)	6,988	2.40 (1.07–5.40)
P-value for interaction				0.34
Hormone use −				
Adenocarcinoma	55		9	
Person-years	158,847	1.00	24,204	1.28 (0.60–2.73)
Hormone use +				
Adenocarcinoma	8		6	
Person-years	21,431	1.23 (0.59–2.58)	6,978	2.71 (1.12–6.58)
P-value for interaction				0.41

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

Early and long-term exposure to endogenous estrogen may contribute to an elevated risk of lung cancer, as may drastic changes in estrogen concentration due to intervention in menstruation and exogenous estrogen use in later life. Several previous studies have reported an increase in lung cancer risk after hysterectomy[3,6,16] and that this was highest among women whose ovaries remained intact, suggesting a role for estrogen concentration in the etiology of lung cancer.[3] Although we did not collect data on whether the ovaries, uterus or both were removed in the present study, given that 75% of women with induced menopause had a history of endometritis or myoma of the uterus, whereas 9% had ovaritis, it is reasonable to think that most women with induced menopause had undergone hysterectomy, at which time the ovaries are also usually removed. Although estrogen concentration is generally considered an etiologic factor for lung cancer among surgically menopausal women, one US study that noted an increased risk for hysterectomy suggested that hysterectomy may be associated, either directly or indirectly, with venous thrombi in the pelvic veins, which may produce multiple showers of small emboli in the lungs, resulting in localized proliferative changes in the bronchial epithelium.[3] In our study, the proportion of hormone replacement therapy among surgically menopausal women was twice that in naturally menopausal women. The finding of only a slightly increased risk for lung cancer among induced menopausal women without hormone replacement therapy *vs.* a markedly elevated risk among induced women with hormone replacement therapy strongly suggests that risk is elevated by hormone use itself rather than any surgery-related effect. In contrast, however, hormone replacement therapy was not associated with an increased risk of lung cancer among naturally menopausal women. This apparent discrepancy might have resulted from differences in total dosages of hormones used between surgically and naturally menopausal women, particularly if both the daily dosage administered and length of administration was higher in the former, as seems likely. A second explanation may be that, with the loss of the major organ of sex hormone receptors, the uterus, opportunities for excess estrogens to bond with receptors in the lung might increase among surgically menopausal women when exogenous estrogens are used, which might in turn stimulate the epithelium of the lung to act as a lung tumor promoter. A previous study reported that the blood concentration of estrogen among women undergoing hysterectomy without removal of the ovaries was elevated and that their risk of lung cancer increased correspondingly.[3] These data support our second hypothesis concerning the influence of uterus resection and imply that the lung might be an estrogen-responsive organ.

An interesting finding was a drastic and linear decrease in age at menarche occurring over a period of only 26 years. Women aged 65–69 at baseline (born in 1924–29) began menstruation at a mean age of 16.0 years. In those aged 40–44 years (born in 1945–50), in contrast, mean age had decreased to 13.6 years. This finding confirms a trend identified in a previous Japanese study[17] and is the result of marked improvements in social and economic living conditions in the last century.

The predominant use of estrogen replacement therapy later in life and the observed increase in risk of lung cancer after induced menopause and use of estrogen suggest a role for exogenous estrogens in the promotion phase of carcinogenesis. However, the high risk for early menarche and late menopause, but not for a long period of menstruation alone, imply that female hormones might also be involved in the initiation stage of lung cancer. Estrogens may influence lung cancer development, either through the direct promotion of cell proliferation in the lung or as a result of an effect on lung-carcinogen metabolism or the development of lung diseases that predispose to lung cancer. Estrogens could act as promoters through a receptor-mediated mechanism. The presence of estrogen receptors (ERα and ERβ) has been reported in lung tumors[18,19] and to a lesser extent in normal lung tissue.[20] Lung tumors from women are more likely to express receptors than those from men,[20] and adenocarcinomas showed higher expression than squamous cell carcinomas.[10] Endogenous and exogenous estrogens have also been implicated as a cause of lung cancer without receptor activation; in this case they may represent direct-acting carcinogens, after metabolic activation to catechol estrogens, which can form DNA adducts.[21]

There was a marked difference between the 2 cohorts in the proportion of hormone use. Hormone replacement therapy was not a common practice in Japan until the last few decades. In Cohort II, the proportion of women aged 40–49 years with experience of hormone use was almost 4 times that of women aged 60–69 years. Thus, fewer women in Cohort II, who were on average older than those in Cohort I, received hormone replacement therapy. In addition, the definition of "hormone use" differed between the 2 cohorts, partly resulting in different proportions of hormone users. Some misclassification may thus have been inevitable, although the results of hormone use and induced menopause relative to the risk of total lung cancer and adenocarcinoma of the lung showed no substantial change when the 2 cohorts were analyzed separately or in combination. Another limitation of our study is that no baseline information on the type, duration of use or dosage of female hormone use was collected and thus the association of hormone factors with lung cancer could not be confirmed by further analysis on dose-response relationships. We have no data on the percentage of women using hormones for the treatment of menstrual disorders, either during or outside of menopause. Since oral contraceptives were rarely used in Japan when the subjects were at reproductive age, the influence of oral contraceptives did not need to be considered in our study. Passive smoking was moderately associated with lung cancer risk in this subgroup (data not shown), but "passive smoking from current family members" was not eli-

cited in our questionnaire, and so only passive smoking in the workplace and passive smoking from family members during childhood were considered as covariates for adjustment. We did not observe any interaction between passive smoking and reproductive variables or hormone use. The number of lung cancer cases was relatively low, especially after analysis was restricted to menopausal women, making the study of relatively low statistical power. Further studies are warranted to confirm our findings.

The observation of an increased risk of adenocarcinoma among induced menopausal women receiving estrogen replacement therapy implies that exogenous steroid hormones may play a role in the etiology of lung cancer in women. In addition, the contribution of endogenous estrogens, suggested by the decreased risk of lung cancer among women with early age at menopause and late age at menarche, provides evidence for our hypothesis that female hormones may be involved in the etiology of lung cancer in women. If these results are confirmed, specific attention should be given to women undergoing induced menopause with hormone replacement therapy, and the necessity of hormone replacement therapy should be carefully considered.

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References

1. Seow A, Poh WT, Teh M, Eng P, Wang YT, Tan WC, Chia KS, Yu MC, Lee HP. Diet, reproductive factors and lung cancer risk among Chinese women in Singapore: evidence for a protective effect of soy in nonsmokers. Int J Cancer 2002;97:365–71.
2. Kreuzer M, Gerken M, Heinrich J, Kreienbrock L, Wichmann HE. Hormonal factors and risk of lung cancer among women? Int J Epidemiol 2003;32:263–71.
3. Wu AH, Yu MC, Thomas DC, Pike MC, Henderson BE. Personal and family history of lung disease as risk factors for adenocarcinoma of the lung. Cancer Res 1988;48:7279–84.
4. Brenner AV, Wang Z, Kleinerman RA, Lei S, Metayer C, Wang W, Lubin JH. Menstrual and reproductive factors and risk of lung cancer among Chinese women, Eastern Gansu Province, 1994–1998. J Epidemiol 2003;13:22–8.
5. Wu-Williams AH, Dai XD, Blot W, Xu ZY, Sun XW, Xiao HP, Stone BJ, Yu SF, Feng YP, Ershow AG, Sun J, Fraumeni JF, Henderson BE. Lung cancer among women in north-east China. Br J Cancer 1990;62:982–7.
6. Taioli E, Wynder EL. Re: Endocrine factors and adenocarcinoma of the lung in women. J Natl Cancer Inst 1994;86:869–70.
7. Adami HO, Persson I, Hoover R, Schairer C, Bergkvist L. Risk of cancer in women receiving hormone replacement therapy. Int J Cancer 1989;44:833–9.
8. Ettinger B, Friedman GD, Bush T, Quesenberry CP Jr. Reduced mortality associated with long-term postmenopausal estrogen therapy. Obstet Gynecol 1996;87:6–12.
9. Schabath MB, Wu X, Vassilopoulou-Sellin R, Vaporciyan AA, Spitz MR. Hormone replacement therapy and lung cancer risk: a case-control analysis. Clin Cancer Res 2004;10:113–23.
10. Omoto Y, Kobayashi Y, Nishida K, Tsuchiya E, Eguchi H, Nakagawa K, Ishikawa Y, Yamori T, Iwase H, Fujii Y, Warner M, Gustafsson JA, et al. Expression, function, and clinical implications of the estrogen receptor beta in human lung cancers. Biochem Biophys Res Commun 2001;285:340–7.
11. Cagle PT, Mody DR, Schwartz MR. Estrogen and progesterone receptors in bronchogenic carcinoma. Cancer Res 1990;50:6632–5.
12. Chaudhuri PK, Thomas PA, Walker MJ, Briele HA, Das Gupta ,TK, Beattie CW. Steroid receptors in human lung cancer cytosols. Cancer Lett 1982;16:327–32.
13. Stabile LP, Davis AL, Gubish CT, Hopkins TM, Luketich JD, Christie N, Finkelstein S, Siegfried JM. Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta and show biological responses to estrogen. Cancer Res 2002;62:2141–50.
14. Yoshimi I, Ohshima A, Ajiki W, Tsukuma H, Sobue T. A comparison of trends in the incidence rate of lung cancer by histological type in the Osaka Cancer Registry, Japan and in the Surveillance, Epidemiology and End Results Program, USA. Jpn J Clin Oncol 2003;33:98–104.
15. Tsugane S, Sobue T. Baseline survey of JPHC study—design and participation rate. Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases. J Epidemiol 2001;11:S24–9.
16. La Vecchia C, Brinton LA, McTiernan A. Menopause, hormone replacement therapy and cancer. Maturitas 2001;39:97–115.
17. Hoshi H, Kouchi M. Secular trend of the age at menarche of Japanese girls with special regard to the secular acceleration of the age at peak height velocity. Hum Biol 1981;53:593–8.
18. Stabile LP, Siegfried JM. Estrogen receptor pathways in lung cancer. Curr Oncol Rep 2004;6:259–67.
19. Kaiser U, Hofmann J, Schilli M, Wegmann B, Klotz U, Wedel S, Virmani AK, Wollmer E, Branscheid D, Gazdar AF, Havemann K. Steroid-hormone receptors in cell lines and tumor biopsies of human lung cancer. Int J Cancer 1996;67:357–64.
20. Fasco MJ, Hurteau GJ, Spivack SD. Gender-dependent expression of alpha and beta estrogen receptors in human nontumor and tumor lung tissue. Mol Cell Endocrinol 2002;188:125–40.
21. Yager JD, Liehr JG. Molecular mechanisms of estrogen carcinogenesis. Annu Rev Pharmacol Toxicol 1996;36:203–32.