Prefectural Chuo-higashi Public Health Center, Tosayamada; H. Sueta, H. Doi, M. Urata, Nagasaki Prefectural Kamigoto Public Health Center, Arikawa; H. Sakiyama, N. Onga, H. Takaesu, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, Osaka Prefectural Suita Public Health Center, Suita; S. Matsushima, S. Natsukawa, Saku General Hospital, Usuda; S. Watanabe, M. Akabane, Tokyo University of Agriculture, Tokyo; M. Konishi, Ehime University, Matsuyama; H. Iso, Y. Honda, Tsukuba University, Tsukuba; H. Sugimura, Hamamatsu University, Hamamatsu; Y. Tsubono, Tohoku University, Sendai; N. Kabuto, National Institute for Environmental Studies, Tsukuba; S. Tominaga, Aichi Cancer Center Research Institute, Nagoya; M. Iida, W. Ajiki, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka; S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, Kochi Medical School, Nankoku; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; Y. Takashima, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; and the late M. Yamaguchi, Y. Matsumura, S. Sasaki, National Institute of Health and Nutrition, Tokyo.

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Cancer Causes and Control 15: 671–680, 2004.

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

Manami Inoue[1,*], Tomotaka Sobue[2] & Shoichiro Tsugane[1] for the JPHC Study Group
[1]*Epidemiology and Prevention Division, Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan;* [2]*Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan*

Received 15 January 2004; accepted in revised form 24 March 2004

Key words: body mass index, cancer incidence, cancer mortality, cohort study, population-based.

Abstract

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

Introduction

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

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

* Study group members are listed in the Acknowledgements at the end of this article.

Address correspondence to: Manami Inoue, MD, PhD, SM, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045 Japan. Ph.: +81 3 3542 2511 Ext 3389; Fax: +81 3 3547 8578; E-mail: mnminoue@gan2.rcs.ncc.go.jp

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

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

Methods

Study population

The Japan Public Health Center-based prospective study on cancer and cardiovascular diseases (JPHC Study) was launched in 1990 for Cohort I and in 1993 for Cohort II. Cohort I was comprised of five prefectural public health center (PHC) areas: Ninohe (Iwate Prefecture), Yokote (Akita Prefecture), Saku (Nagano Prefecture), Chubu (Okinawa Prefecture), and Katsushika (metropolitan Tokyo). Cohort II was comprised of six PHC areas: Mito (Ibaraki Prefecture), Kashiwazaki (Nigata Prefecture), Chuohigashi (Kochi Prefecture), Kamigoto (Nagasaki Prefecture), Miyako (Okinawa Prefecture) and Suita (Osaka Prefecture). The details of the study design have been described elsewhere [12]. The study protocol was approved by the institutional review board of the National Cancer Center, Japan. In the present analysis, the Katsushika and Suita PHC areas were excluded since different definitions of the study population were applied in these areas.

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

Questionnaire

A baseline self-administered questionnaire survey on various lifestyle factors was conducted in 1990 for Cohort I and in 1993–1994 for Cohort II. A total of 95,376 subjects responded to the questionnaire, with a response rate of 82% [13]. Subjects with a present or past history of self-reported serious illness at baseline (cancer, cerebrovascular disease, myocardial infarction, or chronic liver disease) were excluded from further analysis (n = 5073).

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

Follow-up

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

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

The occurrence of cancer was identified by active patient notification from the local major hospitals in the study area and data linkage with population-based cancer registries with permission. Death certificate information was used as a supplementary information source. The location and morphology of each case were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [15]. In our cancer registry system, the proportion of cases for which information was available only from death certificates was 2.3% during the study period. This level of information quality was considered to be satisfactory for the present study. For the present analysis, the earliest date of diagnosis was used in cases with multiple primary cancers at different times. A total of 4756 newly diagnosed cancer cases were identified as of December 31, 2001. We excluded 990 subjects for whom the height and weight data was incomplete and 99 subjects with a BMI of less than 14 or more than 40 because of possibly unreliable data. As a result, 88,927 subjects (42,093 men, 46,834 women), including 4696 incident cancer cases and 1829 cancer deaths, were used for the present analysis.

Analysis

The number of person-years in the follow-up period were counted from January 1st of the baseline survey until the following endpoints: for the analysis of total cancer incidence – the date of occurrence of any cancer, the date of emigration from the study area, the date of death, or the end of the study period (December 31, 2001), whichever came first; for the analysis of total cancer deaths, the date of emigration from the study area, the date of death, or the end of the study period, whichever came first. For persons who were lost to follow-up, the last confirmed date of their presence in the study area was used as the date of censoring.

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

Results

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

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

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

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

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

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

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

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

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The major strength of the present study was its prospective design. Information on the subjects' BMIs were collected before subsequent diagnoses of cancer, thereby avoiding the exposure recall bias that is inherent to case-control studies. We used self-reported heights and weights to obtain the BMIs, but the correlation between these values and those from health screenings was considered to be sufficiently high to minimize BMI misclassification. Change in BMI after the start of the study arising from symptoms related to the subsequent cancer diagnosis may have resulted in some misclassification. Study subjects were selected from the general population, and the response rate of 82% to the baseline questionnaire is acceptable for such a study setting. The proportion of losses to follow-up (0.05%) was negligible during the study period. Although the quality of the cancer registry system was satisfactory over the study period, some geographical variation in the study area occurred. In the present study, we adjusted the study areas in the analysis to control for such geographical variations. We confirmed that the quality of the registry system was not affected by BMI status; therefore, possible misclassification of cancer occurrence by an underreporting of cancer diagnosis would be non-differential and would lead to an underestimation of the results. Since two metropolitan areas were excluded from the present analysis because they used different definitions for the study population, our results may not reflect urban Japanese populations, which is another limitation of the present study. However, the distribution of BMI was not substantially different between the metropolitan and non-metropolitan areas of the study. Therefore, the exclusion of these two metropolitan areas is unlikely to have distorted the present results.

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

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

Acknowledgments

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

This work was supported by a Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare, Japan.

Notes

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

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NUTRITION AND CANCER, 49(1), 32–40

Fish, Long-Chain n-3 Polyunsaturated Fatty Acids, and Risk of Colorectal Cancer in Middle-Aged Japanese: The JPHC Study

Minatsu Kobayashi, Yoshitaka Tsubono, Tetsuya Otani, Tomoyuki Hanaoka, Tomotaka Sobue, and Shoichiro Tsugane for the JPHC Study Group

Abstract: Although long-chain n-3 polyunsaturated fatty acids (Ln-3 PUFA), which are abundant in fish, have shown protective effects on colorectal cancer in laboratory studies, epidemiological studies to date have not been consistent. We evaluated the relationship of consumption of fish and Ln-3 PUFA to the colon and rectal cancer risk in the two cohorts of the Japan Public Health Center-based prospective study of 42,525 men and 46,133 women. Dietary and other exposure data were obtained between 1990 and 1994. Through December 1999, 705 cases of colon and rectal cancer were documented. When data from the two cohorts were pooled, multivariable relative risks (RRs) for the highest quartile compared with the lowest quartile of fish consumption were 1.07 (95% confidence interval, CI = 0.77–1.48) for colon cancer and 0.95 (95% CI = 0.63–1.43) for rectal cancer with no dose-risk trend. RRs for the highest quartile compared with the lowest quartile of eicosapentaenoic acid consumption were 1.05 (95% CI = 0.76–1.46) for colon cancer and 0.91 (95% CI = 0.60–1.38) for rectal cancer with no dose-risk trend. This study does not support the role of fish and Ln-3 PUFA in the etiology of colon and rectal cancer in this population whose fish consumption was high and the variation in Ln-3 PUFA consumption was large.

Introduction

Colorectal cancer is the second most common cause of cancer incidence and mortality in more developed countries. An estimated 945,000 new cases are diagnosed worldwide each year, with 492,000 deaths (1). Lifestyle factors have been suggested to play important roles in its etiology and prevention (2).

From the results of in vitro and in vivo studies, along with those of animal studies, it is evident that long-chain n-3 polyunsaturated fatty acids (Ln-3 PUFA), which are abundant in fish, have protective effects on colorectal cancer (3–5). In contrast, previous epidemiological studies did not provide sufficient evidence for an association between fish intake and colorectal cancer (6,7). Furthermore, only a few studies have examined the association between Ln-3 PUFA and colorectal cancer. In a recent prospective study of Swedish women, none of the specific fatty acids examined were associated with colorectal cancer (8). However, Ln-3 PUFA intake was not so high in the subjects of the Swedish prospective study.

Japanese are characterized by high fish consumption and a large variation in Ln-3 PUFA consumption compared with Western populations (9,10). To further examine the association between fish and Ln-3 PUFA consumption and the risk of colorectal cancer, we conducted a population-based, prospective cohort study in Japan.

Methods

Study Cohort

The Japan Public Health Center-based prospective study on cancer and cardiovascular disease (JPHC study) started in 1990 for Cohort I and in 1993 for Cohort II. Cohort I consisted of five Public Health Center (PHC) areas (Iwate, Akita, Nagano, Okinawa, and Tokyo), and Cohort II consisted of six PHC areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka) across Japan. We excluded the subjects in Tokyo and those in Osaka because different definitions of study population were applied. For the remaining nine PHC areas, study populations were defined to be all inhabitants in the study areas aged 40–59 yr old in Cohort I and 40–69 yr old in Cohort II at the beginning of each study (January 1, 1990, in Cohort I and January 1, 1993, in Cohort II). As a whole, a population-based cohort of 57,714 men (27,063 in Cohort I and 30,651 in Cohort II) and 59,182 women (27,435 in Cohort I and 31,747 in Cohort II) was established. After the initiation of the study, 123 men and 79 women were found to be ineligible and were thus excluded (49 persons of non-Japanese na-

M. Kobayashi, T. Otani, T. Hanaoka, and S. Tsugane are affiliated with the Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan. M. Kobayashi is also affiliated with the Department of Health Care and Nutrition, Showagakuin Junior College, Ichikawa, Japan. Y. Tsubono is affiliated with the School of Public Policy, Tohoku University, Sendai, Japan. T. Sobue is affiliated with the Statistics and Cancer Control Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan.

tionality, 151 with delayed reports of out-migration before the start of the follow-up, and 2 with mistakenly recorded birthdays), leaving 57,591 men and 59,103 women eligible for the study.

Exposure Data

A self-administered questionnaire, which included dietary habits, previous medical history, and other lifestyle factors, was distributed to all registered residents in 1990 for Cohort I and in 1993–1994 for Cohort II (11,12). Among the eligible subjects, 45,452 men (79%) and 49,924 women (84%) responded to the survey.

The average frequency of consumption of 44 food items by Cohort I and 52 food items by Cohort II was reported during the previous month. The Cohort I questionnaire included four items on fish ("fresh fish," "dried and salted fish," "fish roe," and "fermented fish products") and used four categories: almost never, 1–2 days/wk, 3–4 days/wk, and almost daily. The Cohort II questionnaire included six items on fish ("fresh fish," "dried and salted fish," "fermented fish products," "small fry," "fish paste," and "canned fish") and used five categories: never, less than 1 day/wk, 1–2 days/wk, 3–4 days/wk, and almost daily. Information on fish oil supplements was not asked in this study.

Based on 14- to 28-day diet record data, we developed a food composition table that corresponded to the fish items listed in the questionnaire and determined the portion size for each fish item based on the observed median values (13,14). To calculate the amount of fish and Ln-3 PUFA intakes, four items were used in Cohort I, with a portion size of 100 g for fresh fish (9.7 mg of Ln-3 PUFA) in men and 86 g for fresh fish (8.6 mg of Ln-3 PUFA) in women, 20 g for dried and salted fish (3.2 mg of Ln-3 PUFA) in men and 10 g for dried and salted fish (1.7 mg of Ln-3 PUFA) in women, 20 g for fish roe (4.1 mg of Ln-3 PUFA) in men and 17 g for fish roe (3.7 mg of Ln-3 PUFA) in women, and 20 g for fermented fish products (0.9 mg of Ln-3 PUFA) in men and 10 g for fermented fish products (0.5 mg of Ln-3 PUFA) in women. Six items were used in Cohort II, with a portion size of 100 g for fresh fish (7.6 mg of Ln-3 PUFA) in men and 75 g for fresh fish (4.8 mg of Ln-3 PUFA) in women, 48 g for dried and salted fish (5.3 mg of Ln-3 PUFA) in men and 40 g for dried and salted fish (3.7 mg of Ln-3 PUFA) in women, 10 g for fermented fish products (0.4 mg of Ln-3 PUFA) in men and 10 g for fermented fish products (0.4 mg of Ln-3 PUFA) in women, 8 g for small fry (0.2 mg of Ln-3 PUFA) in men and 7 g for small fry (0.2 mg of Ln-3 PUFA) in women, 25 g for fish paste (0.4 mg of Ln-3 PUFA) in men and 23 g for fish paste (0.3 mg of Ln-3 PUFA) in women, and 24 g for canned fish (1.2 mg of Ln-3 PUFA) in men and 20 g for canned fish (0.6 mg of Ln-3 PUFA) in women.

The validity was assessed among subsamples with 14- to 28-day diet record and blood sample. Spearman correlation coefficients between the diet record and the questionnaires of Cohort I (94 men and 107 women) and Cohort II (176 men and 178 women), respectively, were 0.49 in men and 0.45 in women of Cohort I and 0.33 in men and 0.44 in women of Cohort II for the amount of fish intake (g/day), 0.55 in men and 0.54 in women of Cohort I and 0.38 in men and 0.47 in women of Cohort II for calculated eicosapentaenoic acid (EPA) intake (g/day), 0.52 in men and 0.48 in women of Cohort I and 0.44 in men and 0.54 in women of Cohort II for calculated docosahexaenoic acid (DHA) intake (g/day), and 0.50 in men and 0.36 in women of Cohort I and 0.61 in men and 0.61 in women of Cohort II for the ratio of n-3 to n-6 PUFA (Ln-3/n-6 PUFA). These correlation coefficients were improved after adjusting for within-person variability, treating each weekly dietary record as a unit of observation (10). Spearman correlation coefficients between the serum phospholipid level (percent of total fatty acid) and the questionnaire in men of Cohort I ($n = 83$) were 0.54 for EPA and 0.41 for DHA. The average intakes of fish according to quartiles, which was estimated from diet records, were 81.3, 121.3, 150.3, and 195.7 g in men and 66.8, 93.0, 118.4, and 150.2 g in women of Cohort I. The fish intakes averaged 86.1, 115.8, 140.3, and 196.4 g in men and 68.3, 88.1, 106.5, and 131.5 g in women of Cohort II against those from questionnaires: 14.2, 29.9, 56.7, and 92.2 g in men and 13.4, 25.1, 47.2, and 74.3 g in women of Cohort I and 24.6, 44.5, 66.8, and 109.8 g in men and 20.9, 35.3, 49.8, and 80.9 g in women of Cohort II in the same subjects.

Among 45,452 men and 49,924 women who responded to the questionnaire, 687 men and 1,363 women who reported a past history of cancer and 2,240 men and 2,428 women who reported extreme total energy intake (upper 2.5% or lower 2.5%) were excluded, leaving 42,525 men and 46,133 women for the analysis.

Follow-Up

Colorectal cancer incidence data were collected through two data sources, one from local hospitals and the other from population-based cancer registries. Death certificates were used to supplement the information on cancer incidence.

The cancer incidence data and migration data gathered were described in an early report (15). Up to December 31, 1999, 764 new colorectal cancer cases were identified. For multiple primary cancers of the colon or rectum, only the earliest diagnosis was used. Among these incident cases, 705 were pathologically confirmed as adenocarcinoma (M: 8140, 8210, 8211, 8240, 8243, 8260, 8261, 8262, and 8263 according to the *International Classification of Disease for Oncology*, 2nd ed.) (16). Among non-case study subjects, 5.0% moved out of the study area, and 0.04% was lost to follow-up within the study period.

Statistical Analysis

We computed the colorectal cancer incidence rate for a quartile category of fish or Ln-3 PUFA consumption by dividing the number of colorectal cancer cases by person-years of follow-up. Person-years of follow-up were counted from the start of the study periods of January 1, 1990, for Cohort I

and January 1, 1993, for Cohort II until the date of diagnosis of colorectal cancer, death, moving away from a PHC area, or the end of follow-up (December 31, 1999), whichever occurred first. We employed the Cox proportional-hazards regression model to estimate the relative risk (RRs) using the SAS PHREG procedure (17). RRs were adjusted for the following variables: age (5-yr age groups); PHC areas; smoking status (never, former, current); body mass index, BMI (<19, 19, and <23, ≥23 and <27, ≥27); alcohol consumption (none, occasional, <150 g/wk, ≥150 g/wk); leisure time physical activity (less than once a month and once a month or more); use of supplements for vitamin A, C, or E (yes or no); total energy intake and cereal, vegetable, and meat intake (in quartiles); and family history of colorectal cancer (yes or no).

First, we estimated the RRs for colon cancer and rectal cancer in each cohort because the questionnaire makeup was different for Cohort I and Cohort II, respectively. Second, we pooled the results obtained from the two cohorts and calculated the pooled RRs by the use of a fixed-effects model weighting the two RRs by the inverse of the standard error (18). Tests of heterogeneity were used to evaluate whether associations differed between men and women and between Cohorts I and II. For all the associations, no statistically significant heterogeneity was seen. We repeated all the analyses after excluding the 125 colorectal cancer cases diagnosed in the first 2 yr of follow-up (76 men and 49 women). The *P* values for the test of linear trend were two sided.

Results

The distribution of the baseline characteristics according to quartile of fish intake is shown in Table 1. For Cohorts I and II, men with high fish intake were found to have higher alcohol consumption, whereas women with high fish intake were less likely to be current smokers. Participants with high fish consumption also reported a higher intake of total energy, meat, vegetable, and fruit. However, no appreciable difference was observed in cereal consumption. Fish intake was not linearly associated with age, family history of colorectal cancer, BMI, leisure time physical activity, or vitamin supplement use.

RRs of colon and rectal cancer for quartiles of fish and Ln-3 PUFA consumption from each cohort and from combined cohorts are listed in Table 2 for men and in Table 3 for women. Because area- and age-adjusted and fully adjusted RRs were not substantially changed, we present fully adjusted results. For both men and women, intakes of fish, EPA, and DHA were not associated with colon cancer or rectal cancer for Cohorts I and II. No such association was found either when cohorts were combined. In combined cohorts, adjusted RRs for the highest quartile of fish consumption compared with the lowest quartile in men and women, respectively, were 1.07 (95% confidence interval, CI = 0.72–1.58) and 1.05 (95% CI = 0.61–1.82) for colon cancer and 1.31 (95% CI = 0.78–2.22) and 0.69 (95% CI = 0.35–1.36) for rectal cancer with no dose-risk trend. Adjusted RRs for the highest quartile of EPA consumption compared with the lowest quartile in men and women, respectively, were 1.06 (95% CI = 0.71–1.58) and 1.04 (95% CI = 0.60–1.80) for colon cancer and 1.37 (95% CI = 0.81–2.32) and 0.57 (95% CI = 0.29–1.15) for rectal cancer with no dose-risk trend. Ln-3/n-6 PUFA was also not associated with colon cancer or rectal cancer for each cohort and combined cohorts. In combined cohorts, adjusted RRs for the highest quartile of the Ln-3/n-6 PUFA compared with the lowest quartile in men and women, respectively, were 1.08 (95% CI = 0.74–1.56) and 0.92 (95% CI = 0.55–1.54) for colon cancer and 1.26 (95% CI = 0.77–2.05) and 0.61 (95% CI = 0.31–1.19) for rectal cancer with no dose-risk trend.

The null relation between fish, EPA, DHA, and the Ln-3/n-6 PUFA and colon cancer and rectal cancer was consistent when the data of men and women were combined and the data of Cohorts I and II were combined. Adjusted RRs for the highest quartile of fish consumption compared with the lowest quartile were 1.07 (95% CI = 0.77–1.48) for colon cancer and 0.95 (95% CI = 0.63–1.43) for rectal cancer. RRs for the highest quartile of EPA consumption compared with the lowest quartile were 1.05 (95% CI = 0.76–1.46) for colon cancer and 0.91 (95% CI = 0.60–1.38) for rectal cancer with no dose-risk trend.

We next excluded the 125 colorectal cancer cases diagnosed during the first 2 yr of follow-up. None of the results changed substantially (data not shown).

Discussion

In our population-based cohorts of Japanese men and women with high and varied consumption of fish, intake of fish was not associated with any decreased incidence of colon or rectal cancer. Furthermore, we did not obtain evidence of any appreciable benefit from Ln-3 PUFA, such as EPA and DHA, or the Ln-3/n-6 PUFA.

Although the association of total fish consumption with colon and/or rectal cancer incidence has been considered in many previous epidemiological studies, results have not been consistent. Of 15 case-control studies that evaluated the association of fish intake with colon and/or rectal cancer risk, 3 studies found an inverse association (19–21), 2 studies showed results that were inconsistent between men and women (22,23), and 10 studies found no substantial association (24–33). We identified nine prospective studies that evaluated the association of fish intake with colon and/or rectal cancer risk. Our findings are in general agreement with those of eight prospective studies, which show no substantial association with risk of colon and/or rectal cancer (34–41). However, the New York University Women's Health Study showed a significant inverse association for fish intake (42).

There was little evidence of a lower risk of colon and/or rectal cancer with higher intakes of n-3 PUFA. In two case-control studies, one found no substantial association with risk of colon and/or rectal cancer (43), whereas the other study found an inverse association with the consumption of

Table 1. Characteristics of Subjects According to Total Fish Consumption

	Quartiles of Total Fish Consumption							
	Cohort I				Cohort II			
	1 (low)	2	3	4 (high)	1 (low)	2	3	4 (high)
Number of men	5,226	4,345	4,710	5,064	5,665	5,924	5,784	5,807
Age (yr)[a]	49.1 ± 5.9	48.7 ± 6.0	49.5 ± 5.9	50.5 ± 5.9	53.8 ± 9.1	52.3 ± 8.6	53.9 ± 8.7	55.2 ± 8.4
Family history of colorectal cancer (%)	0.7	1.4	1.0	0.8	1.2	1.6	1.4	1.4
Body mass index (kg/m^2)	23.8 ± 2.9	23.3 ± 2.7	23.5 ± 2.7	23.3 ± 2.7	23.5 ± 3.0	23.5 ± 2.9	23.5 ± 2.9	23.5 ± 2.9
Leisure time physical activity (>1 day/month, %)	33.9	35.8	34.5	31.8	31.4	35.4	34.1	29.8
Smoking status (%)								
Never	26.7	21.3	24.9	23.1	26.4	23.9	24.1	23.7
Past	24.6	20.7	23.7	22.0	21.6	23.6	25.4	25.7
Current	48.7	58.0	51.5	54.9	52.0	52.5	50.4	50.6
Alcohol consumption (%)								
None	27.2	18.2	20.9	16.8	32.2	24.4	24.3	22.2
<1 day/week	16.3	9.8	10.5	6.6	11.0	8.6	7.8	6.8
≤150 g/week	19.0	16.9	18.6	15.5	15.8	18.0	16.8	14.6
>150 g/week	37.4	55.2	50.1	61.1	41.0	48.9	51.1	56.3
Vitamin supplement user (%)	5.7	4.5	5.1	6.2	12.5	13.2	13.2	13.1
Total energy intake (MJ)	7.6 ± 2.0	9.0 ± 2.2	8.9 ± 2.1	9.9 ± 2.2	6.3 ± 1.8	7.0 ± 1.8	7.3 ± 1.8	7.8 ± 1.9
Cereal consumption (g)	344.2 ± 109.2	394.1 ± 124.4	377.9 ± 122.9	393.9 ± 126.1	303.2 ± 97.3	319.0 ± 99.8	324.7 ± 102.2	323.9 ± 105.2
Meat consumption (g)	41.8 ± 22.1	43.6 ± 20.8	47.0 ± 23.4	53.0 ± 28.9	20.7 ± 13.7	26.5 ± 13.9	28.1 ± 15.6	29.3 ± 19.4
Vegetable consumption (g)	136.5 ± 88.4	161.3 ± 84.6	177.2 ± 87.0	207.5 ± 100.4	46.6 ± 71.3	57.2 ± 61.5	62.2 ± 67.5	73.8 ± 91.5
Fruit consumption (g)	70.3 ± 85.5	90.0 ± 84.8	94.2 ± 89.4	117.1 ± 122.4	45.0 ± 63.7	55.7 ± 61.6	61.6 ± 67.0	71.1 ± 82.4
Number of women	5,427	4,639	5,459	5,236	6,100	6,584	6,346	6,342
Age (yr)	49.3 ± 5.9	49.3 ± 5.9	49.4 ± 5.8	50.5 ± 5.7	55.2 ± 9.1	53.0 ± 9.1	54.0 ± 8.6	55.5 ± 8.2
Family history of colorectal cancer (%)	0.9	1.0	1.1	0.9	0.7	1.6	1.5	1.3
Body mass index (kg/m^2)	23.8 ± 3.2	23.4 ± 3.1	23.4 ± 3.0	23.5 ± 3.1	23.6 ± 3.4	23.4 ± 3.1	23.5 ± 3.2	23.6 ± 3.3
Leisure time physical activity (>1 day/month, %)	19.8	22	22.3	20.7	24	26.4	26.6	25.7
Smoking status (%)								
Never	91.3	92.3	93.7	94.1	92.2	92.5	93.9	94.0
Past	2.0	1.8	1.6	1.3	1.1	1.0	1.2	1.0
Current	6.7	5.9	4.7	4.6	6.6	6.5	4.9	5.0
Alcohol consumption (%)								
None	83.4	74.6	75.3	76.7	85.6	80.9	81.1	83.1
<1 day/week	10.0	13.0	13.5	11.5	7.1	9.5	8.8	7.0
≤150 g/week	4.9	9.2	9.4	9.0	5.1	7.3	7.6	7.2
>150 g/week	1.7	3.1	1.9	2.9	2.2	2.2	2.5	2.8
Vitamin supplement user (%)	8.5	7.1	7.6	7.7	14.6	15.1	17.2	17.1
Total energy intake (MJ)	5.2 ± 1.1	5.7 ± 1.2	5.9 ± 1.2	6.3 ± 1.2	3.9 ± 0.9	4.4 ± 0.9	4.6 ± 0.9	5.0 ± 0.9
Cereal consumption (g)	218.3 ± 60.7	231.5 ± 64.6	236.9 ± 64.1	235.1 ± 66.3	196.0 ± 51.5	202.1 ± 52.3	205.3 ± 52.7	209.0 ± 54.5
Meat consumption (g)	35.5 ± 19.0	37.4 ± 19.3	38.5 ± 19.7	40.7 ± 24.1	16.9 ± 11.8	21.9 ± 12.1	23.5 ± 13.1	25.3 ± 15.9
Vegetable consumption (g)	148.4 ± 82.1	173.4 ± 81.6	188.6 ± 75.4	207.8 ± 81.7	45.9 ± 59.4	55.5 ± 53.7	62.7 ± 59.2	73.5 ± 74.3
Fruit consumption (g)	98.6 ± 87.3	126.5 ± 90.8	137.3 ± 85.2	148.4 ± 98.6	59.9 ± 62.8	75.4 ± 59.1	85.3 ± 62.7	95.8 ± 66.7

a: Values are reported as means with standard deviations.

Table 2. Multivariate Relative Risks (RR) of Colon and Rectal Cancer According to Fish and N-3 PUFA Consumption: JPHC Study Cohort I Men (1990–1999) and II Men (1993–1999) Combined[a]

	Colon Cancer					Rectal Cancer				
	1 (low)	2	3	4 (high)	Test for Trend *P* Value	1 (low)	2	3	4 (high)	Test for Trend *P* Value
Fish										
Total person-years	84,576	78,034	80,777	85,184						
Total number of cases	63	68	76	93		40	36	29	49	
Median intake (g), Cohort I	21.4	34.2	58.6	104.3						
Median intake (g), Cohort II	15.1	36.4	63.1	111.7						
RR[b] (95% CI), Cohort I	1.00	0.90 (0.54–1.50)	0.99 (0.61–1.61)	0.74 (0.44–1.27)	0.36	1.00	0.68 (0.32–1.44)	0.53 (0.25–1.15)	0.88 (0.42–1.84)	0.75
RR[b] (95% CI), Cohort II	1.00	1.45 (0.82–2.57)	1.46 (0.83–2.57)	1.59 (0.90–2.81)	0.14	1.00	1.72 (0.84–3.53)	1.35 (0.63–2.90)	1.96 (0.94–4.10)	0.14
RR[b] (95% CI), Pooled	1.00	1.11 (0.76–1.63)	1.17 (0.81–1.69)	1.07 (0.72–1.58)	0.73	1.00	1.11 (0.66–1.86)	0.85 (0.50–1.46)	1.31 (0.78–2.22)	0.39
EPA										
Total person-years	81,751	81,744	81,714	83,363						
Total number of cases	61	70	79	90		41	36	26	51	
Median intake (g), Cohort I	0.09	0.17	0.27	0.46						
Median intake (g), Cohort II	0.04	0.11	0.17	0.31						
RR[b] (95% CI), Cohort I	1.00	0.79 (0.47–1.32)	1.01 (0.61–1.69)	0.71 (0.40–1.25)	0.40	1.00	0.74 (0.36–1.52)	0.48 (0.21–1.10)	0.98 (0.45–2.12)	0.99
RR[b] (95% CI), Cohort II	1.00	1.62 (0.92–2.85)	1.46 (0.83–2.59)	1.58 (0.90–2.79)	0.20	1.00	1.37 (0.67–2.78)	1.12 (0.53–2.39)	1.83 (0.90–3.72)	0.14
RR[b] (95% CI), Pooled	1.00	1.09 (0.75–1.60)	1.19 (0.81–1.74)	1.06 (0.71–1.58)	0.74	1.00	1.01 (0.61–1.68)	0.76 (0.43–1.33)	1.37 (0.81–2.32)	0.28
DHA										
Total person-years	81,956	81,639	82,025	82,952						
Total number of cases	65	67	77	91		43	35	28	48	
Median intake (g), Cohort I	0.18	0.28	0.43	0.71						
Median intake (g), Cohort II	0.09	0.20	0.32	0.56						
RR[b] (95% CI), Cohort I	1.00	0.81 (0.49–1.33)	0.89 (0.54–1.48)	0.70 (0.41–1.21)	0.28	1.00	0.73 (0.36–1.50)	0.54 (0.25–1.19)	0.88 (0.41–1.89)	0.76
RR[b] (95% CI), Cohort II	1.00	1.22 (0.69–2.16)	1.38 (0.79–2.40)	1.40 (0.80–2.46)	0.23	1.00	1.12 (0.56–2.25)	0.98 (0.47–2.05)	1.49 (0.74–3.00)	0.33
RR[b] (95% CI), Pooled	1.00	0.97 (0.66–1.41)	1.09 (0.75–1.58)	0.98 (0.66–1.46)	0.93	1.00	0.91 (0.55–1.50)	0.74 (0.43–1.27)	1.17 (0.70–1.96)	0.61
Ln-3/n-6 PUFA										
Total person-years	82,037	81,840	81,962	82,733						
Total number of cases	61	68	78	93		40	31	34	49	
Median intake (g), Cohort I	0.05	0.09	0.12	0.19						
Median intake (g), Cohort II	0.04	0.08	0.12	0.21						
RR[b] (95% CI), Cohort I	1.00	0.94 (0.58–1.52)	1.08 (0.67–1.75)	0.84 (0.51–1.40)	0.61	1.00	1.02 (0.52–2.03)	0.74 (0.35–1.57)	1.17 (0.58–2.38)	0.79
RR[b] (95% CI), Cohort II	1.00	1.22 (0.70–2.13)	1.24 (0.72–2.14)	1.41 (0.83–2.42)	0.23	1.00	0.73 (0.34–1.57)	1.25 (0.64–2.44)	1.34 (0.69–2.63)	0.23
RR[b] (95% CI), Pooled	1.00	1.05 (0.73–1.51)	1.15 (0.80–1.64)	1.08 (0.74–1.56)	0.65	1.00	0.88 (0.53–1.47)	0.99 (0.60–1.64)	1.26 (0.77–2.05)	0.29

a: Abbreviations are as follows: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Ln-3/n-6 PUFA, ratio of long-chain n-3 polyunsaturated fatty acid (EPA+DHA) to n-6 polyunsaturated fatty acid (sum of n-6 polyunsaturated fatty acids).

b: Adjusted for age, area, family history of colorectal cancer, BMI, physical activity, smoking status, alcohol intake, use of vitamin supplement, total energy, cereal, vegetable, and meat intake.

Table 3. Multivariate Relative Risks (RR) of Colon and Rectal Cancer According to Fish and N-3 PUFA Consumption: JPHC Study Cohort I Women (1990–1999) and II Women (1993–1999) Combined[a]

	Colon Cancer					Rectal Cancer				
	1 (low)	2	3	4 (high)	Test for Trend *P* Value	1 (low)	2	3	4 (high)	Test for Trend *P* Value
Fish										
Total person-years	91,779	87,154	93,992	92,577						
Total number of cases	37	34	39	46		29	18	27	21	
Median intake (g), Cohort I	18.4	26.3	48.8	91.8						
Median intake (g), Cohort II	12.3	29.6	49.5	84.3						
RR[b] (95% CI), Cohort I	1.00	0.95 (0.48–1.89)	0.81 (0.40–1.65)	1.10 (0.53–2.25)	0.83	1.00	0.48 (0.17–1.32)	0.99 (0.42–2.35)	0.59 (0.21–1.64)	0.63
RR[b] (95% CI), Cohort II	1.00	1.23 (0.59–2.60)	1.46 (0.70–3.06)	1.00 (0.44–2.31)	0.85	1.00	0.87 (0.39–1.96)	0.79 (0.34–1.85)	0.79 (0.32–1.92)	0.57
RR[b] (95% CI), Pooled	1.00	1.07 (0.65–1.78)	1.08 (0.65–1.79)	1.05 (0.61–1.82)	0.77	1.00	0.69 (0.37–1.30)	0.88 (0.48–1.62)	0.69 (0.35–1.36)	0.46
EPA										
Total person-years	91,349	90,565	91,441	92,147						
Total number of cases	37	37	36	46		30	18	28	19	
Median intake (g), Cohort I	0.08	0.14	0.24	0.41						
Median intake (g), Cohort II	0.03	0.07	0.11	0.20						
RR[b] (95% CI), Cohort I	1.00	0.93 (0.47–1.84)	0.80 (0.38–1.68)	1.03 (0.49–2.16)	0.94	1.00	0.46 (0.18–1.24)	0.92 (0.37–2.25)	0.55 (0.20–1.58)	0.55
RR[b] (95% CI), Cohort II	1.00	1.31 (0.63–2.76)	1.29 (0.61–2.72)	1.06 (0.47–2.39)	0.88	1.00	0.78 (0.34–1.77)	0.88 (0.40–1.96)	0.59 (0.23–1.49)	0.34
RR[b] (95% CI), Pooled	1.00	1.09 (0.66–1.80)	1.02 (0.60–1.71)	1.04 (0.60–1.80)	0.87	1.00	0.63 (0.33–1.18)	0.90 (0.49–1.63)	0.57 (0.29–1.15)	0.27
DHA										
Total person-years	91,175	90,914	91,175	92,238						
Total number of cases	37	33	41	45		29	19	27	20	
Median intake (g), Cohort I	0.15	0.26	0.38	0.64						
Median intake (g), Cohort II	0.07	0.13	0.21	0.35						
RR[b] (95% CI), Cohort I	1.00	0.96 (0.48–1.89)	1.15 (0.57–2.30)	1.17 (0.56–2.45)	0.56	1.00	0.99 (0.40–2.46)	1.30 (0.52–3.27)	0.98 (0.34–2.79)	0.89
RR[b] (95% CI), Cohort II	1.00	1.02 (0.48–2.17)	1.28 (0.61–2.67)	0.99 (0.44–2.22)	0.88	1.00	0.47 (0.19–1.14)	0.80 (0.37–1.76)	0.49 (0.19–1.24)	0.27
RR[b] (95% CI), Pooled	1.00	0.98 (0.59–1.63)	1.21 (0.73–2.00)	1.08 (0.63–1.87)	0.59	1.00	0.67 (0.36–1.27)	0.98 (0.54–1.78)	0.66 (0.33–1.33)	0.47
Ln-3/n-6 PUFA										
Total person-years	91,224	90,198	91,199	92,162						
Total number of cases	35	39	41	41		28	23	25	19	
Median intake (g), Cohort I	0.05	0.09	0.12	0.19						
Median intake (g), Cohort II	0.03	0.06	0.09	0.15						
RR[b] (95% CI), Cohort I	1.00	1.42 (0.74–2.72)	1.03 (0.51–2.08)	1.27 (0.64–2.55)	0.78	1.00	0.72 (0.30–1.73)	0.84 (0.35–2.00)	0.80 (0.32–1.99)	0.72
RR[b] (95% CI), Cohort II	1.00	0.64 (0.29–1.39)	1.29 (0.67–2.46)	0.61 (0.28–1.32)	0.55	1.00	1.07 (0.50–2.27)	1.05 (0.49–2.27)	0.44 (0.17–1.19)	0.16
RR[b] (95% CI), Pooled	1.00	1.02 (0.62–1.68)	1.16 (0.72–1.87)	0.92 (0.55–1.54)	0.84	1.00	0.90 (0.51–1.60)	0.95 (0.57–1.69)	0.61 (0.31–1.19)	0.20

a: Abbreviations are as follows: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; Ln-3/n-6 PUFA, ratio of long-chain n-3 polyunsaturated fatty acid (EPA+DHA) to n-6 polyunsaturated fatty acid (sum of n-6 polyunsaturated fatty acids).

b: Adjusted for age, area, family history of colorectal cancer, BMI, physical activity, smoking status, alcohol intake, use of vitamin supplement, total energy, cereal, vegetable, and meat intake.

n-3 PUFA and a positive association with Ln-6/n-3 PUFA (44). Our findings are in general agreement with three prospective studies that show no substantial association with risk of colon and/or rectal cancer (8,41,45).

It is reported that the protective effects of n-3 PUFA consumption are seen only in areas where fish consumption is high (46). In a recent case-control study, in which participants' fish consumption was relatively high, the protective effects of n-3 PUFA intake were found (44). Although mean daily intakes of fish and Ln-3 PUFA in the present study were higher than those in this case-control study, intakes of fish and Ln-3 PUFA were not associated with a decreased incidence of colon or rectal cancer.

Our questionnaires included only a few fish items, and the estimated portion size might have been small because it was determined based on the observed median values on all fish items from diet record data. Therefore, fish and Ln-3 PUFA intake calculated from the questionnaires were underestimated. However, the correlations between fish and Ln-3 PUFA intake estimated from the questionnaires and those from the 28-day dietary record were reasonably high; also, the correlations between fish and Ln-3 PUFA intake estimated from the questionnaires and Ln-3 PUFA levels of serum phospholipid level appeared high. Thus, the questionnaire appeared to be useful in terms of ranking of subjects, although not so much for absolute intakes. In fact, we earlier observed associations between some dietary factors and the risk of cancer (15,47,48). Therefore, it is unlikely that failure to observe a protective association was due to the crude designs of our questionnaires. However, we could not examine the risk among persons with very low intakes of fish and Ln-3 PUFA because the questionnaire used in the present study complicated the estimation of very low amounts of fish and Ln-3 PUFA intake.

The makeup of Cohort I and Cohort II questionnaires was different in terms of the number of items in the fish and frequency categories. Therefore, the estimated fish and Ln-3 PUFA consumption was different between Cohorts I and II. However, correlations between fish and Ln-3 PUFA intake estimated from the questionnaires and those from the 28-day dietary record were relatively high in both Cohort I and Cohort II.

Our questionnaires did not ask for information on fish oil supplements. However, prevalence of the use of this supplement was only 1.9% among a subgroup of the cohorts who participated in the validation study of the food-frequency questionnaire (Kobayashi, unpublished data). Therefore, the lack of items on fish oil supplements in our questionnaire would not materially distort our observations.

The hypothesis that fish and Ln-3 PUFA might lower the risk of colorectal cancer has been reported (2,49,50). It is known that cyclooxygenase (COX)-1 and COX-2 are among the targets of nonsteroidal anti-inflammatory agents (NSAIDs), and that treatment with NSAIDs is associated with a decrease in COX-2 activity in colon tumors. Ln-3 PUFA inhibits COX-2 and the oxidative metabolism of arachidonic acid to prostaglandin E_2 (PGE_2) (51,52). A recent study reported that retinoid X receptors, a family of nuclear receptors implicated in cancer chemoprevention, are preferentially activated by n-3 PUFA in mouse and human colonocytes (53). On another note, it has been reported that a diet rich in n-6 PUFA increases the frequency of etheno-DNA adducts, which are highly miscoding lesions in mammalian cells and are thought to initiate the carcinogenic process through specific point mutations (54,55). It has also been reported that an increase in n-3 PUFA intake can inhibit the metabolism of n-6 PUFA (5). However, our findings were not consistent with this hypothesis.

It is reported that the shift toward a Western diet usually involves a decrease in n-3 PUFA intake and an increase in n-6 PUFA intake (56). In addition, several animal and human studies reported that reductions in epithelial cell proliferation rates, mammary tumorigenesis, and PGE_2 biosynthesis can best be achieved with a relatively high intake ratio of n-3 to n-6 PUFA (n-3/n-6 PUFA) (57–61). When we calculated the n-3/n-6 PUFA, we did not take into account linolenic acid; hence, the median intake of Ln-3/n-6 PUFA was lower, but the variation was wider than in other studies (43,44). Therefore, it was expected that the possible association between the Ln-3/n-6 PUFA and colon and/or rectal cancer incidence has been clearly shown. Nevertheless, we found no association of the Ln-3/n-6 PUFA with colon and/or rectal cancer.

In conclusion, in a prospective cohort study of middle-aged Japanese, fish and Ln-3 PUFA intake were not associated with colon and/or rectal cancer risk, even though there was a large variation in fish consumption among subjects.

Acknowledgments and Notes

This work was supported in part by a Grant-in-Aid for Cancer Research and a Grant-in-Aid for the Second Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan. Members of the Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases (JPHC Study) Group are S. Tsugane, T. Hanaoka, T. Sobue, National Cancer Center Research Institute, Kashiwa and Tokyo; J. Ogata, S. Baba, T. Mannami, National Cardiovascular Center, Suita; K. Miyakawa, F. Saito, A. Koizumi, Y. Sano, Iwate Prefectural Ninohe Public Health Center, Ninohe; Y. Miyajima, N. Suzuki, S. Nagasawa, Y. Furusugi, Akita Prefectural Yokote Public Health Center, Yokote; H. Sanada, Y. Hatayama, F. Kobayashi, H. Uchino, Y. Shirai, T. Kondo, R. Sasaki, Y. Watanabe, Nagano Prefectural Saku Public Health Center, Saku; Y. Kishimoto, E. Tanaka, M. Kinjo, T. Fukuyama, Okinawa Prefectural Chubu Public Health Center, Ishikawa; K. Imoto, H. Yazawa, T. Seo, A. Seiko, F. Ito, Katsushika Public Health Center, Tokyo; A. Murata, K. Minato, K. Motegi, T. Fujieda, Ibaraki Prefectural Mito Public Health Center, Mito; K. Matsui, T. Abe, Niigata Prefectural Kashiwazaki Public Health Center, Kashiwazaki; M. Doi, Y. Ishikawa, A. Terao, Kochi Prefectural Chuo-higashi Public Health Center, Tosayamada; H. Sueta, H. Doi, M. Urata, Nagasaki Prefectural Kamigoto Public Health Center, Arikawa; H. Sakiyama, N. Onga, H. Takaesu, Okinawa Prefectural Miyako Public Health Center, Hirara; F. Horii, I. Asano, H. Yamaguchi, K. Aoki, S. Maruyama, Osaka Prefectural Suita Public Health Center, Suita; S. Matsushima, S. Natsukawa, Saku General Hospital, Usuda; S. Watanabe, M. Akabane, Tokyo University of Agriculture, Tokyo; M. Konishi, Ehime University, Matsuyama; H. Iso, Y. Honda, Tsukuba University, Tsukuba; H. Sugimura, Hamamatsu University, Hamamatsu; Y. Tsubono, Tohoku University, Sendai; N. Kabuto, National Institute for Environmental Studies, Tsukuba; S. Tominaga, Aichi Cancer Center Research Institute, Nagoya; M. Iida, W. Ajiki, Osaka Medical Center for Cancer and Cardiovascular Disease, Osaka;

S. Sato, Osaka Medical Center for Health Science and Promotion, Osaka; N. Yasuda, Kochi Medical School, Nankoku; S. Kono, Kyushu University, Fukuoka; K. Suzuki, Research Institute for Brain and Blood Vessels, Akita; Y. Takashima, Kyorin University, Mitaka; E. Maruyama, Kobe University, Kobe; and the late M. Yamaguchi, Y. Matsumura, and S. Sasaki, National Institute of Health and Nutrition, Tokyo. We thank Junko Ishihara for contributing the validation study of fatty acid intake. Address correspondence to S. Tsugane, Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, 5–1–1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Phone: +81–3–3547–5879. FAX: +81–3–3547–8578. E-mail: stsugane@ncc.go.jp.

Submitted 18 December 2003; accepted in final form 29 April 2004.

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