Meat, fish and fat intake in relation to subsite-specific risk of colorectal cancer: The Fukuoka Colorectal Cancer Study

Yasumi Kimura,[1,12] Suminori Kono,[1] Kengo Toyomura,[1] Jun Nagano,[1] Tetsuya Mizoue,[1] Malcolm A. Moore,[1] Ryuichi Mibu,[2] Masao Tanaka,[2] Yoshihiro Kakeji,[3] Yoshihiko Maehara,[3] Takeshi Okamura,[4] Koji Ikejiri,[5] Kitaroh Futami,[6] Yohichi Yasunami,[7] Takafumi Maekawa,[8] Kenji Takenaka,[9] Hitoshi Ichimiya[10] and Nobutoshi Imaizumi[11]

Departments of [1]Preventive Medicine, [2]Surgery and Oncology, and [3]Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582; [4]Department of Gastroenterological Surgery, National Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395; [5]Division of Surgery, National Kyushu Medical Center, 1-8-1 Jigyohama, Chuo-ku, Fukuoka 810-8563; [6]Department of Surgery, Fukuoka University Chikushi Hospital, 377-1 Oaza-zokumyoin, Chikushino-shi 818-0067; the [7]First and [8]Second Departments of Surgery, Fukuoka University School of Medicine, 4-45-1 Nanakuma, Jonan-ku, Fukuoka 814-0180; [9]Division of Surgery, Fukuoka City Hospital, 13-1 Yoshizuka-honmachi, Hakata-ku, Fukuoka 812-0046; [10]Division of Surgery, Hamanomachi General Hospital, 3-5-27 Maizuru, Chuo-ku, Fukuoka 810-8539; and [11]Division of Surgery, Fukuoka Red Cross Hospital, 3-1-1 Ogusu, Minami-ku, Fukuoka 815-8555, Japan

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High intake of red meat has been associated with increased risk of colorectal cancer in Western countries. There has been much interest in the role of n-3 polyunsaturated fatty acids (PUFA) in colorectal cancer prevention, but epidemiological findings are limited and inconsistent. The objective of our study was to examine associations of meat, fish and fat intake with risk of colorectal cancer, paying particular attention to the subsite within the colorectum. Data were from the Fukuoka Colorectal Cancer Study, a population-based case-control study, covering 782 cases and 793 controls. Diet was assessed by interview, using newly developed personal-computer software for registering semiquantitative food frequencies. The intake of beef/pork, processed meat, total fat, saturated fat or n-6 PUFA showed no clear association with the overall or subsite-specific risk of colorectal cancer. There was an almost significant inverse association between n-3 PUFA and the risk of colorectal cancer; the covariate-adjusted odds ratio for the highest (median 3.94 g/day) versus lowest (median 1.99 g/day) quintile of energy-adjusted intake was 0.74 (95% confidence interval 0.52–1.06, trend *P* = 0.050). The consumption of fish and fish products was similarly inversely related to the risk although the association was not statistically significant. These associations were more evident for distal colon cancer; adjusted odds ratio for the highest versus lowest quintile of n-3 PUFA intake was 0.56 (95% confidence interval 0.34–0.92, trend *P* = 0.02). Our findings do not support the hypothesis that consumption of red meat increases colorectal cancer risk but do suggest that high intake of fish may decrease the risk, particularly of distal colon cancer. (*Cancer Sci* 2007; 98: 590–597)

Colorectal cancer is one of the most common cancers in the world, accounting for nearly 10% of all incident cases.[1] In Japan, mortality from and incidence of colorectal cancer, especially of colon cancer, have increased markedly over the last decades,[2] and it has been argued that the increase is primarily due to Westernization of the Japanese diet.[3] Of the dietary factors possibly linked with colorectal cancer, fat intake has long been a matter of interest. Substantial data from animal and metabolic studies support a role for dietary fat in colorectal carcinogenesis, with high intake of saturated fat and n-6 polyunsaturated fatty acids (PUFA) documented to increase the incidence of chemically induced colon cancer in animal models.[4,5] However, results from case-control and cohort studies have consistently suggested a null association between total fat intake and colon or colorectal cancer, as reviewed elsewhere extensively.[6,7] It remains uncertain whether saturated or animal fat is related to increased risk of colorectal cancer.[6,7] However, high intake of red meat has been implicated as being associated with an increased risk of colon or colorectal cancer.[8,9]

There has been much interest recently in the role of n-3 PUFA and fish oil in colorectal cancer prevention. Studies in experimental animals have suggested that n-3 PUFA may be protective in colorectal carcinogenesis,[10] but epidemiological findings are limited and inconsistent. A protective association between fish consumption and colorectal cancer was observed in a cohort study of women in New York,[11] and a large cohort study in Europe,[12] but not in other cohort studies in Western countries as noted in a recent review.[13] A case-control study of French Canadians showed a clear protective association between dietary intake of n-3 PUFA and colorectal cancer,[14] whereas other case-control studies have generally failed to find a protective association with fish or n-3 PUFA intake in different countries.[15–17] In Japan, fish consumption was unrelated to colorectal cancer in two cohort studies,[18,19] but one of these found a decreased risk of colorectal cancer in individuals, especially in men, with high concentrations of serum n-3 PUFA.[20] A case-control study in Aichi Prefecture showed a decreased risk of colon cancer in men, but not in women, with high consumption of raw and cooked fish,[21] whereas a subsequent case-control study based on a revised questionnaire failed to find any association of fish and n-3 PUFA intake with either colon or rectal cancer.[22] Interestingly, the same research group recently reported an inverse association of docosahexaenoic acid, as well as of arachidonic acid and total PUFA, in erythrocytes with colorectal cancer in a case-control study.[23]

We here investigated associations of meat of different types, fish and individual types of fatty acids with colorectal cancer risk in the Fukuoka Colorectal Cancer Study.[24] Because these dietary factors may be differentially related to risks of cancer at different subsites of the colorectum,[25,26] we examined associations for the three subsites of the colorectum, that is, proximal colon, distal colon and rectum, separately.

Materials and Methods

The Fukuoka Colorectal Cancer Study is a population-based case-control study designed to examine the relationship of dietary

[12]To whom correspondence should be addressed.
E-mail: ykimura@phealth.med.kyushu-u.ac.jp

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and lifestyle factors to the risk of colorectal cancer. Cases were patients undergoing surgery for a first diagnosis of colorectal cancer, and controls were selected randomly in the community. The study protocol was approved by the ethical committee of the Faculty of Medical Sciences, Kyushu University and those of all but two of the participating hospitals. The two exceptions had no ethical committees at the time of the survey, so permission was granted by their directors. Details of the methods have been reported previously,[24] and methodological matters relevant to the present analysis are described below.

Subjects. Cases consisted of consecutive patients with histologically confirmed incident colorectal adenocarcinomas who were admitted to two university or six affiliated hospitals for surgical treatment during the period from October 2000 to December 2003. Other eligibility criteria were as follows: age of 20–74 years at the time of diagnosis, residents of the study area (Fukuoka City and three adjacent areas), no prior history of partial or total removal of the colorectum, familial adenomatous polyposis or inflammatory bowel disease, and mental competence to give informed consent and participate in the interview. Of 1053 eligible cases, 840 cases (80%) were actually included.

Eligibility criteria for controls were almost the same as for cases except for two items, that is, having no diagnosis of colorectal cancer and age 20–74 years at the time of selection. Numbers of control candidates by sex and 10-year age class were determined in accordance to sex- and age-specific expected numbers of incident cases of colorectal cancer. A total of 1500 control candidates were selected by the method of two-stage random sampling. First 15 small areas corresponding to primary school zones were selected randomly, and then approximately 100 people were chosen randomly for each small area using the municipal resident registry. At most four letters of invitation were sent to each candidate control. A total of 833 people participated in the survey. The net participation rate was calculated as 60% (833/1382), after exclusion of those who were found to be ineligible for the following reasons: death ($n = 7$), migration from the study area ($n = 22$), undelivered mail ($n = 44$), history of large-bowel resection ($n = 21$), mental incompetence ($n = 19$), and diagnosis of colorectal cancer after the survey ($n = 5$).

In the present analysis, we excluded subjects with an extreme energy intake beyond the range of mean ± 2 SD in the log-transformed energy intake in three age categories (<50, 50–69 and 70 years) for each sex. Finally, 782 cases and 793 controls remained. Numbers of subsite-specific colorectal cancers were as follows: proximal colon 177, distal colon 262, rectum 327, and multiple sites 16. The cecum, ascending colon and transverse colon were combined as the proximal colon, and the distal colon comprised the descending and sigmoid colon.

Lifestyle questionnaire. A questionnaire was used for research nurses to carry out a uniform interview with cases and controls regarding multifaceted lifestyle factors except dietary details. In this study, the referent time for cases was the date of the onset of symptoms or the screening, and that for controls was the time of interview. We attempted to avoid ascertainment of lifestyle factors in the immediate past as much as possible, and different time frames were used for different factors primarily for ease of recalling habitual lifestyles in the past. Anthropometric questions inquired about height (cm), recent bodyweight (kg) and bodyweight at the time 10 years before. Body mass index (kg/m^2) 10 years before was used, because the current body mass index was unrelated to the risk.

Questions on physical activities elicited type of job, activities in commuting, housework and shopping, together with leisure-time activities at the time 5 years previously. As regards type of job, five options were prepared: sedentary or standing work, work with walking, labor work, hard labor work and no job. Regular leisure-time activities were ascertained with regularity defined as at least once per week. As for at most three activities, type of activity, numbers of months and of days per week that individuals participated in each activity, and minutes of participation per occasion were reported. As described in detail previously,[27] physical activity in the leisure time (including activities in commuting, housework and shopping) was expressed as the sum of metabolic equivalents (MET) multiplied by hours of participation in each activity, which was thereafter called MET-hours.

With regard to smoking habit, ever-smokers were asked about years of smoking and numbers of cigarettes smoked per day for each decade of age from the second to eighth decade. We calculated the cumulative exposure to cigarette smoking until the beginning of the previous decade of age. Alcohol use at the time of 5 years prior to the referent time was elicited. Individuals answered open-ended questions regarding the frequency of consumption and habitual amount of alcohol consumed on the day of alcohol drinking. The amount of alcohol was expressed in the conventional unit; one *go* (180 mL) of *sake*, one large bottle (633 mL) of beer, and half a *go* (90 mL) of *shochu* were each expressed as one unit; and one drink (30 mL) of whisky or brandy and one glass (100 mL) of wine were each converted to a half unit.

Dietary assessment. A personal-computer (PC) software program was developed for dietary assessment with support from an external laboratory (Core Create Systems, Kitakyushu, Japan). A total of 148 items of foods and beverage were selected with reference to dietary questionnaires developed previously in Japan.[28–30] Consumption frequencies and portion sizes of these foods and beverages were ascertained by interview using the PC software, which was to help individuals report consumption of specific foods and dishes. The collected information was the same as obtained by the so-called semiquantitative food frequency questionnaire. As for consumption frequency, different numbers of response categories were prepared for rice with each meal, other food items, and non-alcoholic and alcoholic beverages. Typical dishes were shown on the display for each food item, together with typical portion sizes. Options for serving size were 0.5, 1, 1.5 and 2 of the size displayed as a reference for most of the food items. Supplementary questions included an inquiry about consumption of fat portions of beef/pork and skin of chicken at table and others. Three precoded answers were prepared for the consumption of fat portion or skin of chicken (all, half or null consumption), and the corresponding foods, such as beef/pork without fat and chicken with skin, were chosen for calculation of nutrients. Beef and pork were combined for most of the questions. Participants were asked to report the consumption on average over the 1 year before the referent time, and controls answered dietary questions with reference to the past 1 year before the interview. After the episode of bovine spongiform encephalopathy (BSE) in the year 2001,[31] individuals were carefully instructed to provide answers for consumption before change of dietary habits if it had recently occurred.

Based on the interview data, 148 food/dish items in the PC software were collapsed into 211 food items to calculate nutrient intake. Some items in the PC software were dishes and collective foods (such as beef/pork and ham/sausage), and individual foods of such composite items were separated on the basis of typical recipes and market statistics. Of these 211 food items, 202 items corresponded to foods listed in the food composition tables in Japan.[32] An appropriate food could not be assigned to the remaining nine items (five groups of fish for different ways of cooking, miso, vegetables oils, oranges other than mandarin and pickles of non-green vegetables), and composition data were created on the basis of diet records derived from a validation study carried out with 28 subjects aged 41–65 years (13 men and 15 women), who had participated as controls in the present case-control study. Diet records were done over a period of 7 days in four consecutive seasons in accordance with the method used elsewhere.[28] A total of 60 people were asked to participate in

Table 1. Characteristics of cases and controls

Characteristics	Case (n = 782)	Control (n = 793)
Male (%)	60.5	62.4
Age (years), mean (SD)	61 (9)	59 (11)
Residence, rural (%)	39.8	35.9
BMI 10 years before (kg/m^2), mean (SD)	23.3 (3.2)	22.9 (3.1)
Parental colorectal cancer (%)	7.7	5.6
Ever-smoking (%)		
Male	82.5	81.8
Female	15.2	21.8
Alcohol use (%)[†]		
Male	77.6	78.2
Female	28.5	30.2
Non-sedentary job (%)	26.0	30.5
Leisure-time physical activity (%)[‡]	62.7	66.2
Nutrients and foods, median (IQR)[§]		
Total energy (kcal/day)	2185 (1819–2552)	2196 (1814–2606)
Total fat (g/day)	62 (52–70)	62 (54–71)
Red meat (g/day)[¶]	43 (29–61)	45 (29–61)
Fish and fish products (g/day)	77 (54–102)	78 (56–104)
Calcium (mg/day)	647 (519–777)	664 (521–813)
Total fiber (g/day)	14.5 (11.7–17.5)	14.5 (11.9–17.7)

[†]Drinking alcohol at least once per week. [‡]Physical activity of moderate or greater intensities (metabolic equivalent ≥4). [§]Energy-adjusted intake calculated by the regression residual method. [¶]Beef/pork and processed meat combined. BMI, body mass index; IQR, interquartile range; SD, standard deviation.

the validation study. Of them, 35 started to record their diet, and the above 28 people completed the diet records. Details of the validation study will be described elsewhere (in preparation). Pearson correlation coefficients of energy-adjusted intake (see below) of selected nutrients and foods estimated from the two methods were as follows: total fat 0.70, saturated fat 0.72, n-6 PUFA 0.41, n-3 PUFA 0.34, beef/pork 0.70, processed meat 0.57, and fish and fish products 0.21. Beef/pork and processed meat were combined as red meat in the present study.

Statistical analysis. Intakes of foods and nutrients were adjusted for energy intake by the regression residual method with intake values transformed to the natural-log scale.[33] Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence intervals (CI) to assess the relationship of fat and meat intake to colorectal cancer risk. Nutrient and food intake were categorized into five levels using the quintiles of each nutrient or food intake in the control group. The trend of the association was assessed with ordinal scores 0–4 assigned to five categories in order. All P-values were two-sided, and considered significant at $P < 0.05$. All analyses were conducted using the Statistical Analysis System (SAS) version 8.2 (SAS Institute, Cary, NC, USA).

Potential confounding factors under consideration were 5-year age class (the lowest class of <40 years), sex, residence area (Fukuoka City or the adjacent areas), body mass index (kg/m^2) 10 years before (<25.0 or ≥25.0 kg/m^2), parental colorectal cancer, smoking (0, 1–399, 400–799 or ≥800 cigarettes/year), alcohol intake (0, 0.1–0.9, 1.0–1.9, or ≥2.0 units/day), type of job (sedentary or non-sedentary), leisure-time physical activity (0, 1–15.9 or ≥16 MET-hours/week) and dietary calcium and fiber (quintiles).

Results

Table 1 summarizes characteristics of cases and controls with respect to potential confounders and some of the factors under study. Occupational and leisure-time physical activity were slightly lower in the cases than in the controls. Body mass index was slightly greater and parental colorectal cancer was more frequent in the cases. Smoking and alcohol use did not vary much according to case-control status in either men or women. Median intake of calcium was lower in the cases, but there was no appreciable difference in total energy intake, total fat, red meat, fish and fish products, and dietary fiber.

Crude and adjusted OR of colorectal cancer did not differ from unity according to consumption levels of beef/pork, processed meat or poultry (Table 2). Total, saturated and monounsaturated fat also showed no clear association with the overall risk (Table 2). Intake of n-6 PUFA seemed to be related to a decreased risk of colorectal cancer, but the decreasing trend was far from statistical significance in the multivariate analysis ($P = 0.17$). As shown in Table 3, the OR decreased progressively with higher intake of n-3 PUFA, and the decrease was almost statistically significant even after full adjustment for the confounding variable ($P = 0.050$). A similar, but less clear, inverse association was noted for the consumption of fish and fish products.

In the subsite-specific analysis, beef/pork, processed meat and poultry showed no clear association with cancer of the proximal colon, distal colon or rectum (Table 4). Again, different types of fatty acids (excluding n-3 PUFA) were unrelated to subsite-specific risks of colorectal cancer. A statistically significant inverse association with n-3 PUFA was observed only for distal colon cancer (Table 5). The subsite-specific analysis also revealed a decreased risk of distal colon cancer associated with the consumption of fish and fish products, showing a nearly significant trend ($P = 0.052$).

Discussion

The present study showed no clear association between red meat or associated fat intake and colorectal cancer in a large case-control study and thus did not provide support for the hypothesis that high consumption of red meat increases the risk of colorectal cancer at any subsite. However, there was an inverse association between n-3 PUFA intake and colorectal cancer, especially distal colon cancer.

High consumption of red meat was shown to be associated with a modest increase in the risk of colorectal cancer in a meta-analysis of studies in Western countries, although findings from

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Table 2. Meat and fat intake and risk of colorectal cancer

Food and nutrient (quintile)[†]	Median (g/day)	No. controls	No. cases	OR[‡]	OR (95% CI)[§]
Beef/pork					
Q1	14.2	158	142	1.00	1.00
Q2	27.3	159	188	1.35	1.35 (0.98–1.85)
Q3	37.4	158	161	1.23	1.28 (0.92–1.79)
Q4	48.6	159	140	1.04	1.03 (0.73–1.44)
Q5	70.1	159	151	1.16	1.13 (0.80–1.61)
Trend		159	151	$P = 0.95$	$P = 0.94$
Processed meat					
Q1	0.4	158	152	1.00	1.00
Q2	2.5	159	149	1.02	1.03 (0.74–1.43)
Q3	4.9	158	160	1.10	1.09 (0.79–1.52)
Q4	8.2	159	151	1.07	1.07 (0.77–1.49)
Q5	14.9	159	170	1.20	1.15 (0.83–1.60)
Trend				$P = 0.25$	$P = 0.40$
Red meat[¶]					
Q1	18.0	158	154	1.00	1.00
Q2	32.3	159	174	1.14	1.14 (0.83–1.57)
Q3	44.5	158	166	1.15	1.13 (0.82–1.57)
Q4	57.4	159	122	0.86	0.84 (0.60–1.19)
Q5	78.9	159	166	1.19	1.14 (0.81–1.62)
Trend				$P = 0.84$	$P = 0.97$
Poultry					
Q1	5.2	158	178	1.00	1.00
Q2	12.0	159	153	0.88	0.88 (0.64–1.21)
Q3	17.0	158	138	0.82	0.79 (0.57–1.09)
Q4	23.5	159	176	0.99	0.92 (0.67–1.26)
Q5	35.0	159	137	0.81	0.75 (0.54–1.05)
Trend				$P = 0.41$	$P = 0.17$
Total fat					
Q1	45.7	158	185	1.00	1.00
Q2	55.6	159	158	0.85	0.91 (0.66–1.26)
Q3	62.0	158	146	0.78	0.86 (0.61–1.20)
Q4	69.6	159	161	0.84	0.97 (0.69–1.37)
Q5	78.2	159	132	0.71	0.77 (0.53–1.13)
Trend				$P = 0.08$	$P = 0.33$
Saturated fatty acids					
Q1	11.39	158	170	1.00	1.00
Q2	14.55	159	186	1.08	1.19 (0.86–1.64)
Q3	16.65	158	144	0.83	0.90 (0.64–1.26)
Q4	19.08	159	133	0.76	0.86 (0.60–1.23)
Q5	22.10	159	149	0.88	1.04 (0.71–1.51)
Trend				$P = 0.12$	$P = 0.52$
Monounsaturated fatty acids					
Q1	15.29	158	180	1.00	1.00
Q2	19.11	159	160	0.90	0.97 (0.70–1.33)
Q3	21.52	158	151	0.85	0.95 (0.68–1.32)
Q4	24.33	159	148	0.82	0.91 (0.65–1.28)
Q5	28.06	159	143	0.83	0.88 (0.62–1.25)
Trend				$P = 0.22$	$P = 0.44$
n-6 PUFA					
Q1	7.98	158	194	1.00	1.00
Q2	10.19	159	152	0.81	0.82 (0.59–1.13)
Q3	11.63	158	150	0.79	0.83 (0.60–1.16)
Q4	13.10	159	145	0.73	0.77 (0.55–1.09)
Q5	15.23	159	141	0.71	0.77 (0.54–1.10)
Trend				$P = 0.04$	$P = 0.17$

[†]Energy-adjusted intake calculated by the regression residual method. [‡]Adjusted for age, sex and residential area. [§]Adjusted for age, sex, residential area, body mass index 10 years before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium and dietary fiber. [¶]Beef/pork and processed meat combined. CI, confidence interval; OR, odds ratio; PUFA, polyunsaturated fatty acids.

Table 3. Fish and fish products, n-3 polyunsaturated fatty acid (PUFA) intake and risk of colorectal cancer

Food and nutrient (quintile)†	Median (g/day)	No. controls	No. cases	OR‡	OR (95% CI)§
Fish and fish products					
Q1	37.4	158	164	1.00	1.00
Q2	61.1	159	159	0.88	0.93 (0.67–1.29)
Q3	77.5	158	168	0.90	0.89 (0.64–1.24)
Q4	98.2	159	143	0.75	0.77 (0.55–1.07)
Q5	138.1	159	148	0.77	0.80 (0.57–1.13)
Trend				$P = 0.07$	$P = 0.11$
n-3 PUFA					
Q1	1.99	158	172	1.00	1.00
Q2	2.55	159	177	0.99	1.02 (0.74–1.40)
Q3	2.92	158	152	0.84	0.89 (0.64–1.23)
Q4	3.29	159	149	0.80	0.84 (0.60–1.18)
Q5	3.94	159	132	0.68	0.74 (0.52–1.06)
Trend				$P = 0.01$	$P = 0.05$

†Energy-adjusted intake calculated by the regression residual method. ‡Adjusted for age, sex and residential area. §Adjusted for age, sex, residential area, body mass index 10 years before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium and dietary fiber. CI, confidence interval; OR, odds ratio.

Table 4. Meat and fat intake and subsite-specific risk of colorectal cancer

Food and nutrient consumption†	Proximal colon cancer		Distal colon cancer		Rectal cancer	
	n	OR (95% CI)‡	*n*	OR (95% CI)	*n*	OR (95% CI)
Beef/pork						
Q1	23	1.00	54	1.00	63	1.00
Q2	48	2.21 (1.26–3.88)	65	1.24 (0.80–1.94)	73	1.18 (0.78–1.79)
Q3	41	2.00 (1.12–3.58)	46	0.94 (0.58–1.52)	70	1.18 (0.77–1.81)
Q4	35	1.67 (0.91–3.06)	41	0.80 (0.49–1.31)	57	0.88 (0.56–1.38)
Q5	30	1.44 (0.76–2.71)	56	1.23 (0.75–2.00)	64	1.01 (0.64–1.60)
Trend		$P = 0.64$		$P = 0.97$		$P = 0.64$
Processed meat						
Q1	40	1.00	48	1.00	59	1.00
Q2	27	0.82 (0.47–1.44)	49	1.10 (0.68–1.78)	70	1.20 (0.78–1.84)
Q3	35	1.12 (0.65–1.92)	57	1.30 (0.81–2.08)	64	1.08 (0.69–1.67)
Q4	33	1.04 (0.60–1.80)	49	1.15 (0.71–1.86)	68	1.21 (0.78–1.87)
Q5	42	1.20 (0.72–2.03)	59	1.32 (0.82–2.11)	66	1.14 (0.73–1.77)
Trend		$P = 0.33$		$P = 0.27$		$P = 0.61$
Red meat§						
Q1	27	1.00	56	1.00	69	1.00
Q2	46	1.74 (1.01–3.00)	58	1.03 (0.65–1.61)	68	0.98 (0.65–1.49)
Q3	43	1.69 (0.97–2.95)	48	0.84 (0.53–1.35)	68	1.01 (0.66–1.54)
Q4	29	1.21 (0.66–2.21)	39	0.77 (0.47–1.27)	50	0.70 (0.45–1.11)
Q5	32	1.27 (0.69–2.33)	61	1.28 (0.79–2.07)	72	1.05 (0.67–1.65)
Trend		$P = 0.96$		$P = 0.66$		$P = 0.71$
Poultry						
Q1	39	1.00	65	1.00	71	1.00
Q2	36	0.91 (0.54–1.54)	46	0.71 (0.45–1.12)	66	0.92 (0.60–1.39)
Q3	30	0.83 (0.48–1.45)	51	0.81 (0.51–1.27)	55	0.72 (0.46–1.11)
Q4	40	0.94 (0.56–1.59)	58	0.86 (0.56–1.34)	75	0.94 (0.62–1.42)
Q5	32	0.87 (0.50–1.49)	42	0.65 (0.41–1.05)	60	0.78 (0.51–1.20)
Trend		$P = 0.69$		$P = 0.22$		$P = 0.35$
Total fat						
Q1	34	1.00	74	1.00	74	1.00
Q2	32	1.03 (0.59–1.79)	56	0.86 (0.55–1.35)	67	0.89 (0.58–1.36)
Q3	31	0.94 (0.53–1.68)	41	0.65 (0.40–1.06)	68	0.92 (0.59–1.41)
Q4	50	1.52 (0.88–2.62)	49	0.81 (0.50–1.32)	61	0.89 (0.57–1.40)
Q5	30	0.90 (0.48–1.70)	42	0.70 (0.41–1.20)	57	0.78 (0.48–1.27)
Trend		$P = 0.64$		$P = 0.20$		$P = 0.39$
Saturated fatty acids						
Q1	31	1.00	63	1.00	73	1.00
Q2	36	1.19 (0.68–2.08)	67	1.24 (0.79–1.94)	78	1.06 (0.70–1.60)

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Table 4. *continued*

Food and nutrient consumption†	Proximal colon cancer		Distal colon cancer		Rectal cancer	
	n	OR (95% CI)‡	*n*	OR (95% CI)	*n*	OR (95% CI)
Q3	43	1.45 (0.83–2.55)	44	0.82 (0.50–1.35)	55	0.75 (0.48–1.17)
Q4	36	1.08 (0.60–1.96)	36	0.70 (0.41–1.18)	58	0.85 (0.54–1.35)
Q5	31	0.99 (0.52–1.88)	52	1.17 (0.69–1.99)	63	1.00 (0.62–1.64)
Trend		$P = 0.84$		$P = 0.68$		$P = 0.63$
Monounsaturated fatty acids						
Q1	40	1.00	62	1.00	74	1.00
Q2	28	0.80 (0.46–1.38)	64	1.21 (0.78–1.88)	65	0.87 (0.57–1.32)
Q3	35	0.96 (0.56–1.64)	53	1.09 (0.68–1.74)	59	0.81 (0.53–1.26)
Q4	38	0.98 (0.57–1.66)	40	0.80 (0.48–1.31)	68	0.97 (0.63–1.50)
Q5	36	0.99 (0.56–1.73)	43	0.92 (0.55–1.55)	61	0.84 (0.53–1.34)
Trend		$P = 0.84$		$P = 0.34$		$P = 0.67$
n-6 PUFA						
Q1	32	1.00	77	1.00	81	1.00
Q2	35	1.12 (0.64–1.96)	52	0.71 (0.46–1.11)	60	0.78 (0.51–1.19)
Q3	39	1.29 (0.74–2.24)	41	0.62 (0.39–1.00)	68	0.88 (0.58–1.35)
Q4	33	1.05 (0.58–1.92)	48	0.72 (0.45–1.17)	61	0.77 (0.49–1.19)
Q5	38	1.29 (0.70–2.35)	44	0.67 (0.40–1.12)	57	0.69 (0.43–1.10)
Trend		$P = 0.52$		$P = 0.16$		$P = 0.16$

†Energy-adjusted intake calculated by the regression residual method. ‡Adjusted for age, sex, residential area, body mass index 10 years before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium and dietary fiber. §Beef/pork and processed meat combined. CI, confidence interval; OR, odds ratio; PUFA, polyunsaturated fatty acids.

Table 5. Fish and fish products, n-3 polyunsaturated fatty acid (PUFA) intake and subsite-specific risk of colorectal cancer

Food and nutrient† (quintile)	Proximal colon cancer		Distal colon cancer		Rectal cancer	
	n	OR (95% CI)‡	*n*	OR (95% CI)	*n*	OR (95% CI)
Fish and fish products						
Q1	39	1.00	59	1.00	65	1.00
Q2	32	0.81 (0.47–1.39)	53	0.86 (0.54–1.36)	71	1.03 (0.68–1.58)
Q3	39	0.82 (0.48–1.39)	56	0.84 (0.53–1.33)	70	0.94 (0.62–1.45)
Q4	33	0.71 (0.41–1.23)	48	0.68 (0.42–1.10)	58	0.82 (0.52–1.28)
Q5	34	0.68 (0.38–1.20)	46	0.64 (0.39–1.06)	63	0.91 (0.57–1.43)
Trend		$P = 0.17$		$P = 0.05$		$P = 0.40$
n-3 PUFA						
Q1	31	1.00	74	1.00	65	1.00
Q2	35	1.17 (0.66–2.07)	56	0.79 (0.51–1.23)	82	1.22 (0.80–1.85)
Q3	41	1.28 (0.74–2.24)	41	0.56 (0.35–0.91)	68	1.05 (0.68–1.61)
Q4	41	1.25 (0.71–2.20)	49	0.68 (0.43–1.09)	53	0.76 (0.48–1.20)
Q5	29	0.84 (0.45–1.55)	42	0.56 (0.34–0.92)	59	0.88 (0.56–1.41)
Trend		$P = 0.67$		$P = 0.02$		$P = 0.16$

†Energy-adjusted intake calculated by the regression residual method. ‡Adjusted for age, sex, residential area, body mass index 10 years before, parental colorectal cancer, smoking, alcohol use, type of job, leisure-time physical activity, dietary calcium and dietary fiber. CI, confidence interval; OR, odds ratio.

individual studies were not necessarily consistent.[8,9] Variable results were also reported more recently.[12,34,35] A more evident increase in the risk associated with red meat was noted for distal colon cancer,[26] or rectal cancer,[8,12,25,35] in several studies in Western countries. In Japan, no clear positive association with red meat or individual types of meat was observed for either the overall risk of colorectal cancer or subsite-specific risk.[18,36,37] The present study failed to find any measurable increase in the risk of subsite-specific cancer associated with red meat. However, it should be noted that red meat consumption was relatively low in the present study population (mean intake 50 g/day), which was fairly comparable to that reported in the recent National Nutrition Surveys (mean intake 56 g/day).[38] In Europe and the USA,[12,39,40] the highest consumption levels of red meat ranged from 130 to 160 g/day. In the Japanese population, red meat intake may not have been high or diverse enough to detect a substantive difference in the risk of colorectal cancer.

As mentioned above, epidemiological studies are rather disparate in their findings on the relationship of n-3 PUFA and fish intake to colorectal cancer. The inconsistency may be ascribed to differences in the accuracy of measurement of n-3 PUFA and fish intake. In this context, it is particularly notable that two Japanese studies found a decreased risk of colorectal cancer in those with high levels of n-3 PUFA in sera or erythrocytes.[20,23] The present findings add to evidence that high intake of n-3 PUFA is protective against the occurrence of colorectal cancer. A relatively higher range of fish consumption in the Japanese population compared with Western populations may provide an

advantageous opportunity of addressing the role of n-3 PUFA in colorectal carcinogenesis.

Experimental data are fairly strong regarding the protective role for n-3 PUFA in colorectal carcinogenesis. Fish oil or n-3 PUFA inhibit chemically induced colorectal carcinogenesis in rodents.[41,42] Several mechanisms have been postulated regarding the protective effects of n-3 PUFA.[10,43] High intake of n-3 PUFA suppresses the production of arachidonic acid-derived eicosanoids such as prostaglandin E_2 and leukotriene B_4 due to the change in relative proportions of n-6 and n-3 PUFA in cell membranes.[43] Prostaglandin E_2 increases production of inflammatory cytokines and growth factors that can facilitate tumor growth, invasion and metastasis.[44] Inhibition of cyclooxygenase-2 (COX-2) expression by n-3 PUFA is a mechanistic link of recent interest.[44] Enhanced apoptosis is one of the most important processes linked with the decreased expression of COX-2, although much remains to be clarified with regard to signal transduction downstream of COX-2.[10] It is also suggested that n-3 PUFA suppress the expression of inducible nitric oxide synthetase (NOS) and nuclear transcription factor κB (NF-κB).[43] Inducible NOS is an enzyme involved in the generation of free radicals, and increases DNA damage.[44] NF-κB is deemed to play a crucial role in carcinogenesis by modulating the expression of cell-cycle genes, apoptosis inhibitors and invasive proteases.[45]

In the present study, the intake of n-3 PUFA and fish was most evidently related to a decreased risk of distal colon cancer. Site-specific analysis is of interest because different molecular alterations have been implicated in carcinogenesis of the proximal and distal sites of the colorectum. Genetic alterations such as *K-ras* and *p53* mutations were shown to be more frequent in the distal site, whereas microsatellite instability appears to be almost exclusively associated with proximal colon cancer.[46,47]

The use of community controls, the large size and the high participation rates of both cases and controls are among the advantages of the present study. It is noteworthy that the dietary survey was conducted by in-person interview using PC software. The estimated intake of nutrients and foods seemed to be fairly valid, although caution is needed in extrapolating the results from the validation study, in which the subjects were relatively few and were not selected randomly. Because of the small number of subjects, sex-specific validation was rather difficult. Furthermore, participants completing the diet record may have differed from non-participants in various aspects. A limitation was the retrospective assessment of dietary and other lifestyle factors. Diet in the recent past was used in the present study, but this may not have represented long-term habitual consumption relevant to the development of colorectal cancer. Another concern is the potential effect of the BSE episode on the dietary survey.[31] Beef consumption decreased after the first case of BSE was reported in September 2001 in Japan. Per capita daily intake of beef in the National Nutrition Surveys was 20.5 g/day in the year 2000, 11.3 g/day in 2001 and 14.7 g/day in 2002. However, the consumption of total red meat did not change much due to reciprocal increases of pork and processed meat. The per capita daily intake of pork and processed meat combined for the years 2000, 2001 and 2002 was 36.9 g, 42.0 g and 41.2 g, respectively.[38]

In summary, the Fukuoka Colorectal Cancer Study, a large case-control study in Japan, has provided further evidence that diets high in fish and n-3 PUFA reduce the risk of colorectal cancer, particularly in the distal colon.

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