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Marine n-3 and saturated fatty acids in relation to risk of colorectal cancer in Singapore Chinese: A prospective study

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Abstract

Experimental data support multiple roles for fatty acids in colorectal carcinogenesis. We examined dietary fatty acids and incidence of colorectal cancer, and evaluated effect modification by sex and stage of disease among a population-based cohort of 61,321 Singapore Chinese that was established between 1993 and 1998. As of December 31, 2005, 961 incident colorectal cancers were diagnosed. Presented hazard ratios (HRs) are for highest *versus* lowest quartiles with adjustment for potential confounders. Among women, we observed a dose-dependent, positive association between saturated fat and localized colorectal cancer (Dukes A or B) [(HR = 1.69, 95% confidence interval (CI) = 1.08–2.63, *p* for trend = 0.01)]. No such associations were noted in men (*p* for interaction by sex = 0.04). Marine n-3 polyunsaturated fatty acid (PUFA) intake was positively associated with advanced disease (Dukes C or D) (HR = 1.33, 95% CI = 1.05–1.70, *p* for trend = 0.01), regardless of sex. The association with marine n-3 PUFAs was strongest among those with the shortest (≤5 years) duration of follow-up (HR = 1.49, 95% CI = 1.00–2.21, *p* for trend = 0.04). In contrast, we observed a small, albeit imprecise, inverse association with marine n-3 PUFAs for localized colorectal cancer among those with the longest duration of follow-up (>10 years) (HR = 0.62, 95% CI = 0.29–1.34, *p* for trend = 0.55). Our findings suggest that subtypes of fatty acids may differentially influence risk of colorectal cancer of a specified stage.

Keywords

colorectal cancer; dietary fat; epidemiology; marine n-3 polyunsaturated fatty acids; saturated fatty acids

Dietary fatty acids are related to colorectal carcinogenesis by different mechanisms, depending on their structural classification. Saturated fatty acids increase colorectal cancer risk by indirectly increasing exposure to secondary bile acids.[1] *In vitro* evidence implicates secondary bile acids as risk factors at the early, initiating stages of colorectal carcinogenesis.[2,3] Prospective epidemiologic data from US and European populations both report no association with colorectal cancer for saturated fat,[4,5] and positive associations for saturated fat[6] and for red meat,[7,8] a major source of dietary saturated fat in Western populations.

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Experimental data support a positive association with n-6 PUFAs[9] and an inverse association with marine n-3 PUFAs[10] for colorectal cancer. Cyclooxygenase (COX)-2 catalyzes the synthesis of proinflammatory eicosanoids from arachidonic acid (C20:4n-6).[11] These eicosanoids are involved in colorectal cancer cell proliferation and angiogenesis, or later stages of colorectal carcinogenesis.[11,12] The marine n-3 PUFA, eicosapentaenoic acid, inhibits the formation of proinflammatory eicosanoids, in part by competing with arachidonic acid for access to the COX-2 enzyme.[13,14]

Prospective data for PUFAs in relation to colorectal cancer are fewer, compared to those for saturated fatty acids. However, systematic reviews of prospective cohort data equivocally report both slightly reduced risk between fish and colorectal cancer,[15,16] and no association with marine n-3 PUFAs.[17] A reason for the largely null epidemiologic findings, despite the experimental evidence supporting a role for marine n-3 PUFAs, is that most epidemiologic studies have been conducted among static populations with a low level and/or narrow range of fish intake.[18] As for the lack of convincing epidemiologic data for dietary fat and colorectal cancer in general, few prospective data have been powered to assess fatty acid subgroups by stage of disease.

The Singapore Chinese are a population in transition from a traditional, largely plant- and fish-based diet to one resembling the higher animal fat diet common in Western populations. These dietary changes coincide with improvements in socioeconomic development,[19] and may play a role in the population's increasing colorectal cancer incidence. To address hypotheses conceived from experimental and epidemiologic evidence, we evaluated associations between fatty acid intake and incidence of colorectal cancer, and modification by sex and stage of disease among a prospective cohort of Singapore Chinese.

Material and methods

Study population

The design of the Singapore Chinese Health Study has been previously described in detail.[20] Briefly, the cohort consisted of 63,257 men and women recruited between April 1993 and December 1998, from permanent residents or citizens of Singapore aged 45–74 years, and who resided in government-built housing estates (86% of the Singapore population resided in such facilities). We restricted the study to individuals belonging to the two major dialect groups of Chinese in Singapore: the Hokkiens and the Cantonese. Enrollment in the cohort entailed completing a baseline in-person interview in the participant's home. The questionnaire elicited information on diet, demographics, current physical activity, reproductive history (women only), occupational exposure and medical history. For these analyses, we used data from the 61,321 individuals who did not have a history of cancer diagnosis at baseline, based on self-report and linkage with the Singapore Cancer Registry. The Institutional Review Boards at the University of Minnesota and the National University of Singapore have approved this study.

Identification of incident colorectal cancer cases and deaths among cohort members were accomplished by record linkage of the cohort database with respective databases from the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The nationwide cancer registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases.[21] To date, only 17 cases were known to be lost to follow-up due to migration out of Singapore. As of December 31, 2005 (an average of 9.8 years of follow-up), 961 cohort participants developed invasive colorectal cancer (591 colon cancers, 370 rectal/rectosigmoid cancers). Nine hundred and three (94%) of cases were histologically confirmed as having Dukes A (n = 139), B (n = 247), C (n = 279), or D (n = 248), while the remaining cases were confirmed via review of medical records by a medically

trained research staff or identified through death certificates. We defined localized cases as having either Dukes A or B, and advanced cases as having either Dukes C or D.

Dietary assessment

At baseline, we used a 165-item quantitative food frequency questionnaire (FFQ) to assess usual diet over the past year. Details regarding the development and validation of the FFQ in this population have been published.[22] All pairs of nutrient intake values from the 24-hr recalls and food-frequency questionnaire were within 10% deviation from each other.[22] The FFQ listed 14 seafood items, including fresh fish (fish ball or cake, deep fried fish, pan or stir fried fish, boiled or steamed fish), fresh shellfish (shrimp or prawn, squid or cuttlefish), dried/salted fish (salted fish, ikan bilis, dried fish, other dried seafoods such as dried shrimp, dried oyster, dried cuttlefish), and canned fish (canned tuna, canned sardine). The average portion weight (without bone) for fresh fish was approximately 60 g and for fresh shellfish, dried/salted fish, and canned fish approximately 35, 10, and 60 g, respectively. The island of Singapore is situated one degree north of the equator. Thus, fatty acid composition for fish intake was derived from the commonly consumed warm water, or lean fish species. To adjust for energy intake, all nutrients were expressed in weight unit per 1000 kcal or percentage of total energy, and total energy was included in the adjusted models.

Statistical methods

Person-years of follow-up were counted from the date of recruitment to the date of diagnosis of colorectal cancer, death, migration, or December 31, 2005, whichever occurred first. We examined the relationships of dietary total, saturated, monounsaturated (MUFA), polyunsaturated fat (PUFA), animal fat, and plant fat intakes with risk of colorectal cancer, and with risk of colon and rectal cancer separately. We then separated PUFAs into n-3 and n-6 fatty acids. N-3 PUFAs were further categorized by marine and other food sources.

Proportional hazards regression methods were used to examine the associations between dietary exposure levels and colorectal cancer risk, measured by hazard ratios (HRs) and their corresponding 95% confidence intervals (CIs).[23] Study subjects were grouped into quartiles based on the distribution among the entire cohort, since cutpoints were similar when examined among men and women separately. The linear trend tests for diet-colorectal cancer associations were based on ordinal values of the quartiles (0, 1, 2, 3). In all analyses, we adjusted for the following potential confounders: sex (in analyses involving both sexes), age at baseline interview (years), year of interview (1993–1995, 1996–1998), dialect group (Cantonese, Hokkien), level of education (no formal education, primary school, secondary school or higher), cigarette smoking ("heavy" = started to smoke before age 15 and smoked $\geq$ 13 cigarettes per day, "light" = all nonheavy smokers, never),[24] alcohol consumption (nondrinker, <7 drinks/week, $\geq$7 drinks/week),[24] body mass index (<20, 20–23.9, 24–27.9, $\geq$28 m/kg^2), familial history of colorectal cancer (no, yes first degree relative), diabetes at baseline (no, yes),[25] and any weekly physical activity (no, yes). Additional inclusion of the following dietary variables did not materially change any of the study results: total meat, preserved meat, preserved (*e.g.* dried and salted) fish, nitros-amines, dietary fiber, or folate. Prevalence of vitamin and/or mineral supplement use was low (8%) in our study population. Use of nonsteroidal anti-inflammatory drugs was not collected at baseline. However, data obtained from our follow-up questionnaire indicated that only 6% of the cohort reported regular use, defined as two or more times per week for 1 month or longer in the past year. The follow-up questionnaire was conducted between 1999 and 2004 among 83% of the original cohort, and did not include a dietary assessment.

Based on previous analyses in our data, and reports from the literature, we examined whether the association between fatty acids intake and colorectal cancer varied by the following factors:

sex, tumor site (colon, rectum), stage of disease (local, advanced), BMI (<20, 20–23.9, 24–27.9, ≥28 m/kg^2), education (no formal education, primary school, secondary school or higher), and physical activity (yes/no weekly vigorous activity) by assessing the fitness of interaction terms in adjusted models. We used the Poisson regression methods[26] to compare the estimated rate ratios (RRs) between localized and advanced stage of colorectal cancer in relation to different levels of dietary fatty acids. Similarly, in order to evaluate the internal validity of our findings by stage of disease, we used the Poisson regression methods to examine the differential RRs by the duration of follow-up. Based on previous analyses in our data, we chose to evaluate duration of follow-up by <5, 5–10, and ≥10 years.

Among Singapore Chinese, knowledge of colorectal cancer screening was low,[27] therefore colorectal cancer typically presents with symptoms, such as rectal bleeding and abdominal pain and change in bowel habits.[28] To evaluate the potential for dietary misclassification among symptomatic subjects, we re-ran our findings after excluding the first 12 months or 48 weeks of follow-up. This was a conservative estimate, given that a median duration of 7 weeks (interquartile range = 1–30 weeks) from symptom onset to physician visit has been previously reported in an unscreened population.[28] Statistical computing was conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC). All *p* values were two-sided.

Results

The distribution of selected covariates are presented across quartiles of total fat intake, stratified by sex (Table I). Median age and percentage of light or heavy smokers decreased with increasing total fat intake. Among men, percentage of those who consumed ≥7 drinks per week decreased with increasing total fat. A positive relation was observed between all nutrient variables and total fat intake, such as total energy (r = 0.17), saturated fat (r = 0.80), marine n-3 PUFAs (r = 0.29), and n-6 PUFAs (r = 0.58). Pan-frying is the most common cooking method for fish in our study population. Thus, unlike other populations, fish intake was positively correlated with fat intake (r = 0.35) among Singapore Chinese.

Among the entire cohort, there was no association with total fat, saturated fat, MUFA, animal fat or plant fat intake for colorectal cancer, overall or by subsite (data not shown). However, after stratification by sex and stage of disease, statistically significant trends were observed among women for localized colorectal cancer with total fat, saturated fat, and MUFA intake (Table II). These associations for localized disease were somewhat stronger in the colon subsite (HR = 2.41, 95% CI = 1.39–4.18, *p* for trend = 0.01, for highest *versus* lowest total fat; HR = 1.84, 95% CI = 1.08–3.11, *p* for trend = 0.02 for highest *versus* lowest saturated fat; HR = 2.32, 95% CI = 1.34–4.01, *p* for trend = 0.01 for highest *versus* lowest MUFA). No comparable associations were observed among men. The aforementioned results for localized disease did not change after additional adjustment for marine n-3 PUFAs, and were not modified by duration of follow-up, BMI, physical activity, or education, nor did they change after exclusion of the first 12 months of follow-up (data not shown).

No associations were observed between total PUFAs and colorectal cancer, overall, or when stratified by sex (data not shown). Among the PUFA subgroups, only marine n-3 PUFA intake was associated with colorectal cancer (HR = 1.22, 95% CI = 1.02–1.45, *p* for trend = 0.03 for highest *versus* lowest quartile). We observed that the statistically significant positive association was confined to those with advanced disease (Table III), and was similar among men and women (Table IV). The association with marine n-3 PUFA intake did not change after additional adjustment for saturated fat or MUFA, and was also similar by subsite, BMI, physical activity, and education, and did not change after excluding the first 12 months of follow-up (data not shown).

Based on experimental evidence for an interaction between n-3 and n-6 PUFAs in the COX-2 pathway,[14] we investigated the association with ratio of marine n-3 to n-6 PUFA intake. We observed a positive association with marine n-3/n-6 PUFAs overall, and for advanced disease (Table III). The magnitude of association for advanced disease was similar by sex (Table IV) and subsite (data not shown).

If our data were internally consistent with respect to the suggestive late-acting effects of marine n-3 PUFAs, we would expect that the highest risk would be observed in subjects with advanced disease and the shortest duration of follow-up, in other words, the shortest estimated interval between diet exposure assessment and disease diagnosis. That was indeed what we observed (Table V). There was a statistically significant trend with marine n-3 PUFAs for advanced disease among those with ≤5 years of follow-up. This association remained after excluding the first 12 months of follow-up (HR = 1.49, 95% CI = 1.04–2.14, p for trend = 0.04 for highest *versus* lowest quartile). Interestingly, among all subjects with ≥10 years of follow up, there was a somewhat reduced risk for those in the highest *versus* lowest quartile of marine n-3 PUFA intake (Table V). Similar findings were observed for marine n-3/n-6 PUFA intake by duration of follow-up for advanced disease (data not shown).

Discussion

Our analyses of dietary fatty acids in relation to risk of colorectal cancer revealed two main findings. First, saturated fat was associated with localized, or early-stage, colorectal cancer among women in our prospective cohort of Singaporean Chinese. Second, among the entire cohort, marine n-3 PUFA intake was associated with advanced, or late-stage, colorectal cancer. This latter association was strongest among those with the shortest time interval between baseline diet assessment and cancer diagnosis, demonstrating internal consistency with our data. In summary, our findings suggest that subtypes of fatty acids may differentially influence risk of colorectal cancer of a specified stage.

Our findings for saturated fat and localized disease were consistent with evidence for an early-acting effect of saturated fat on colorectal carcinogenesis.[1,29,30] Although most prospective epidemiologic studies report no association with saturated fat and colorectal cancer,[4,7,31–33] a positive association was reported among a US prospective cohort of women.[6] In contrast to the finding among US women,[6] red meat intake or compounds in cooked meat, such as heterocyclic amines (HAAs) were not likely explanations for our observed positive association with saturated fat. For example, red meat was not the major source of dietary saturated fat, and animal fat from red meat was not associated with colorectal cancer in our data. In addition, it was reported that only nondetectable to low levels of HAAs were produced from stir-frying meat,[34] the primary mode of cooking among Singapore Chinese.

Our findings of no association with saturated fat among men could be the result of residual confounding by alcohol intake. As a risk factor for colorectal cancer in our data,[24] alcohol intake was also inversely correlated with saturated fat intake in men, whereas the majority of the women were nondrinkers. Alcohol and saturated fat were both associated with colorectal tumors characterized by chromosomal and/or microsatellite instability.[35–37] This shared mechanism could lead to an attenuation of the association between saturated fat and colorectal cancer among men in our data.

In addition to saturated fat, we also observed a positive association with MUFA intake. We attribute this association to the strong correlation between saturated fat and MUFA intake in these data (r = 0.76). The difficulty in teasing out the effects of these strongly correlated fatty acids from food frequency data has been observed in another study.[38]

Our second main finding was a positive association between marine n-3 PUFA intake and advanced-stage colorectal cancer, especially for high marine n-3/n-6 PUFA intake. Although the preponderance of experimental data is in favor of a beneficial effect of marine n-3 PUFAs on colorectal carcinogenesis,[10] there exists biologic plausibility for an adverse effect as well. It has been shown that rats with transplanted colon cancer cells had 10-fold more metastases in number and 1000-fold in volume when fed a marine n-3 PUFA diet, compared to either a low-fat or n-6 PUFA diet.[39] The mechanism by which fish oil promotes colon cancer metastases in rat liver may be due to enhanced uptake of purines seen among cancer cells treated with fish oil,[40] and/or downregulation of the immune system by fish oil.[41,42]

Overall, prospective epidemiologic data do not support a role for dietary n-3 PUFAs on risk of colorectal cancer.[17] Null findings have been reported for populations with among the highest colorectal cancer incidence, regardless of whether they had relatively low (*e.g.* US[7,43,44]) or high (*e.g.* Sweden[45] and Japan[46]) fish intake, the major source of n-3 PUFAs. However, in a prospective study of Japanese an inverse association was reported for plasma measures of n-3 PUFAs, among men.[47] The association was not observed among women,[47] although the correlations between diet recall and plasma levels were similar by sex in this population.[48] Our contradictory findings to those from other populations with high fish intake may be due in part to the pattern of intake (*e.g.* small portions at nearly every meal),[49] and/or the fish type (*e.g.* lean species) among Singapore Chinese, or imprecise measure of n-3 PUFA intake.

Animal data suggest that marine n-3 PUFAs play a role in inhibiting colorectal tumor initiation.[50] Thus, a very long follow-up would be needed in order to observe the early-acting protective effects from observational data. Recently, with an average of 22 years of follow-up, a statistically significant inverse association was reported among a US male cohort.[51] In support of an early-acting protective effect of marine n-3 PUFAs, we reported a small, inverse association among subjects with the longest duration of follow up (≥10 years). However, this finding should be interpreted cautiously as it was based on few cases, and thus did not achieve statistical significance.

Strengths of our study include the assessment of fatty acid intake prior to disease diagnosis in a population with a non-Western diet high in vegetables and fish, and low in red meat, the use of an FFQ that was developed for and validated in our population,[22] and the good correlation between FFQ- and 24-hr recall fat intake levels.[22] However, we cannot exclude the possibility of differential misclassification of diet due to undiagnosed disease at baseline, since colorectal cancer screening was not conducted. In addition, although we had sufficient power to assess modification of fatty acid-colorectal cancer associations by sex, subsite and stage of disease, there was a small possibility that multiple comparisons may have led to chance findings. Limitations include our reliance on self-reported dietary and covariate information, so nondifferential misclassification may still be an issue.

Our data support the notion of a late-acting adverse effect of marine n-3 PUFAs for colorectal cancer, and a possible early-acting beneficial effect. Establishing the beneficial and adverse effects of marine n-3 PUFAs is important not only for populations with high fish consumption, but also for populations where fish oil supplementation is common. More laboratory data are needed in order to elucidate the potential adverse effect of marine n-3 PUFAs, before secondary chemoprevention trials for colorectal adenomas or cancer can be considered.

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Abbreviations

CI
: confidence interval

COX
: cyclooxygenase

DHA
: docosahexaenoic acid

EPA
: eicosapentanoic acid

FFQ
: food frequency questionnaire

HAA
: heterocyclic amine

HRs
: hazard ratios

IQR
: inter-quartile range

MUFA
: monounsaturated

PUFA
: polyunsaturated fatty acid

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TABLE I

DISTRIBUTION OF SELECTED BASELINE CHARACTERISTICS STRATIFIED BY SEX AND QUARTILES (Q) OF TOTAL FAT INTAKE

	Men (*N* = 27,293)					Women (*N* = 34,028)				
	Q1	**Q2**	**Q3**	**Q4**	***p* value[a]**	**Q1**	**Q2**	**Q3**	**Q4**	***p* value[1]**
Total fat										
Median value (g/1000 kcal)	18.3	23.3	26.9	31.5	<0.001	18.9	23.4	27.0	31.7	<0.001
Person-years	75,991	66,257	62,552	55,346	–	74,328	85,267	88,178	91,842	–
Median age (IQR)[2] (years)	57 (13)	56 (13)	55 (13)	54 (13)	<0.001	58 (13)	56 (13)	55 (12)	53 (11)	<0.001
Highest level of education (%)										
No formal education	14.6	10.6	9.2	8.0		52.7	43.4	37.3	30.6	
Primary education	56.0	52.8	49.7	44.0		35.3	39.5	41.1	39.6	
Secondary education or higher	29.4	36.6	41.1	48.0	<0.001	12.0	17.1	21.7	29.8	<0.001
Body mass index (kg/m^2) (%)										
<20.0	16.4	15.7	15.4	15.5		15.4	14.5	14.4	14.8	
20.0–24.0	55.9	53.1	52.9	49.7		57.3	55.6	54.1	53.0	
24.1–28.0	22.3	25.3	25.6	27.0		20.5	22.0	23.4	23.5	
>28.0	5.5	5.9	6.2	7.8	<0.001	6.8	7.9	8.1	8.8	<0.001
Smoking history[3], %										
Nonsmoker	39.6	42.2	44.6	43.2		88.9	91.2	92.1	92.5	
Light smokers	51.9	50.2	48.2	49.3		10.3	8.2	7.5	7.0	
Heavy smokers	8.5	7.6	7.2	7.5	<0.001	0.8	0.6	0.4	0.5	<0.001
Alcohol consumption, %										
Nondrinkers	67.5	68.4	68.9	69.9		92.0	92.5	90.6	89.0	
<7 drinks/week	18.5	22.5	24.6	25.2		6.3	6.2	8.2	10.1	
≥7 drinks/week	14.1	9.2	6.5	5.0	<0.001	1.8	1.3	1.1	1.0	<0.001
Diabetes, % yes	6.9	8.6	8.5	11.3	<0.001	8.1	8.8	9.3	10.1	<0.001
Any weekly physical activity, % yes	41.4	44.0	44.4	43.7	0.001	21.7	24.7	25.1	26.9	<0.001
First degree relative with colorectal cancer, % yes	1.9	2.2	2.4	2.7	0.019	1.5	1.9	2.2	2.8	<0.001
Median energy intake, kcal/day (IQR)[1]	1651 (808)	1553 (696)	1658 (650)	1852 (834)	<0.001	1184 (489)	1291 (460)	1355 (571)	1487 (675)	<0.001

	Men (*N* = 27,293)					Women (*N* = 34,028)				
	Q1	**Q2**	**Q3**	**Q4**	***p* value[a]**	**Q1**	**Q2**	**Q3**	**Q4**	***p* value[1]**
Median daily intake, g/1000 kcal (IQR)[1]										
Saturated fat	6.3 (2.1)	8.3 (1.8)	9.8 (2.0)	11.7 (2.5)	<0.001	6.3 (2.1)	8.3 (2.1)	9.7 (2.4)	11.6 (2.8)	<0.001
Monounsaturated fat	6.1 (1.5)	7.9 (1.0)	9.2 (1.1)	10.9 (1.6)	<0.001	6.2 (1.4)	7.8 (1.0)	9.1 (1.1)	10.8 (1.6)	<0.001
Polyunsaturated fat (PUFA)	3.3 (1.4)	4.3 (1.7)	4.8 (1.9)	5.6 (2.2)	<0.001	3.6 (1.6)	4.4 (1.9)	5.1 (2.2)	5.9 (2.6)	<0.001
Total n-3 PUFA	0.38 (0.13)	0.46 (0.13)	0.51 (0.14)	0.55 (0.15)	<0.001	0.40 (0.13)	0.48 (0.13)	0.53 (0.14)	0.59 (0.16)	<0.001
Marine n-3 PUFA	0.14 (0.10)	0.17 (0.10)	0.19 (0.11)	0.20 (0.11)	<0.001	0.15 (0.10)	0.18 (0.11)	0.20 (0.11)	0.21 (0.12)	<0.001
Other foods n-3 PUFA	0.23 (0.09)	0.28 (0.09)	0.31 (0.09)	0.35 (0.10)	<0.001	0.24 (0.09)	0.29 (0.09)	0.32 (0.10)	0.37 (0.11)	<0.001
Total n-6 PUFA	2.9 (1.4)	3.8 (1.7)	4.3 (1.9)	5.0 (2.2)	<0.001	3.1 (1.6)	3.9 (1.9)	4.5 (2.1)	5.2 (2.5)	<0.001
Marine n-3/n-6 PUFA	0.04 (0.04)	0.04 (0.03)	0.04 (0.03)	0.04 (0.03)	<0.001	0.04 (0.04)	0.04 (0.03)	0.04 (0.03)	0.04 (0.03)	<0.001
Total animal fat (from red meat)	2.0 (1.6)	2.8 (1.9)	3.4 (2.2)	4.4 (2.9)	<0.001	1.6 (1.5)	2.3 (1.8)	2.9 (2.0)	3.6 (2.6)	<0.001
Total plant fat	11.6 (3.5)	14.9 (3.3)	17.0 (3.8)	19.9 (4.8)	<0.001	12.9 (3.5)	16.0 (3.2)	18.3 (3.6)	21.5 (4.7)	<0.001
Dietary fiber	10.7 (6.4)	12.1 (7.0)	12.9 (7.3)	14.3 (8.2)	<0.001	9.4 (6.0)	10.7 (6.2)	11.8 (6.7)	13.1 (7.4)	<0.001
Folate	81 (35)	92 (36)	97 (34)	101 (34)	<0.001	83 (36)	95 (36)	102 (37)	109 (38)	<0.001

[1] From χ^2 test for categorical variables and Mann-Whitney Test for continuous variables.

[2] IQR = interquartile range.

[3] Heavy smokers are defined as those who smoked an average of ≥13 cigarettes per day, starting before age 15. Light smokers are nonheavy smokers.

TABLE II

HAZARD RATIO (HR) FOR QUARTILES (Q) OF DIETARY FATTY ACIDS IN RELATION TO COLORECTAL CANCER AMONG MEN AND WOMEN

	Men					Women				
	Median value (g/1000 kcal)	Localized[1]		Advanced[2]		Median value (g/1000 kcal)	Localized[1]		Advanced[2]	
		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]
Total fat										
Q1	18.3	63	1.0 (Ref)	103	1.0 (Ref)	18.9	33	1.0 (Ref)	63	1.0 (Ref)
Q2	23.3	64	1.23 (0.87–1.74)	69	0.79 (0.58–1.08)	23.4	45	1.38 (0.88–2.17)	70	1.12 (0.79–1.57)
Q3	26.9	49	1.06 (0.73–1.55)	74	0.96 (0.71–1.30)	27.0	38	1.26 (0.79–2.02)	56	0.96 (0.66–1.38)
Q4	31.5	34	0.90 (0.59–1.38)	45	0.70 (0.49–1.00)	31.7	50	1.86 (1.18–2.92)	47	0.88 (0.60–1.30)
p for trend			0.63		0.14			0.01		0.40
Saturated fat										
Q1	5.9	62	1.0 (Ref)	102	1.0 (Ref)	6.0	37	1.0 (Ref)	71	1.0 (Ref)
Q2	7.9	64	1.22 (0.86–1.73)	81	0.92 (0.69–1.24)	7.9	40	1.20 (0.77–1.88)	61	0.93 (0.66–1.31)
Q3	9.6	50	1.06 (0.73–1.54)	57	0.72 (0.52–0.99)	9.6	43	1.43 (0.92–2.23)	55	0.91 (0.64–1.30)
Q4	11.8	34	0.85 (0.56–1.30)	51	0.76 (0.54–1.07)	11.9	46	1.69 (1.08–2.63)	49	0.88 (0.61–1.28)
p for trend			0.47[4]		0.04			0.01[4,5]		0.50[5]
MUFA[6]										
Q1	6.0	58	1.0 (Ref)	90	1.0 (Ref)	6.2	33	1.0 (Ref)	63	1.0 (Ref)
Q2	7.8	53	1.09 (0.75–1.58)	76	0.98 (0.72–1.33)	7.8	48	1.48 (0.95–2.31)	68	1.10 (0.78–1.55)
Q3	9.1	57	1.28 (0.89–1.85)	76	1.08 (0.79–1.47)	9.1	38	1.27 (0.79–2.03)	48	0.84 (0.57–1.22)
Q4	10.9	42	1.07 (0.72–1.60)	49	0.78 (0.55–1.11)	10.9	47	1.72 (1.09–2.70)	57	1.07 (0.74–1.54)
p for trend			0.49		0.35			0.05		0.90
Animal fat (from red meat)										
Q1	1.1	49	1.0 (Ref)	54	1.0 (Ref)	1.1	49	1.0 (Ref)	71	1.0 (Ref)
Q2	2.2	52	0.95 (0.64–1.40)	68	1.10 (0.77–1.57)	2.2	46	1.10 (0.73–1.64)	62	1.03 (0.73–1.44)
Q3	3.3	56	1.00 (0.68–1.47)	89	1.38 (0.98–1.94)	3.3	38	1.04 (0.68–1.60)	54	1.03 (0.72–1.47)
Q4	5.2	53	0.87 (0.59–1.29)	80	1.16 (0.82–1.64)	5.0	33	1.09 (0.70–1.70)	49	1.12 (0.77–1.61)
p for trend			0.57		0.25			0.75		0.58
Plant fat										
Q1	11.5	71	1.0 (Ref)	113	1.0 (Ref)	11.9	35	1.0 (Ref)	51	1.0 (Ref)

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	Men					Women				
	Median value (g/1000 kcal)	Localized[1]		Advanced[2]		Median value (g/1000 kcal)	Localized[1]		Advanced[2]	
		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]
Q2	15.0	65	1.19 (0.85–1.66)	84	0.96 (0.72–1.28)	15.1	44	1.07 (0.69–1.67)	68	1.13 (0.79–1.63)
Q3	17.7	37	0.84 (0.56–1.25)	51	0.71 (0.51–0.99)	17.8	42	1.00 (0.64–1.57)	59	0.96 (0.66–1.40)
Q4	21.5	37	1.13 (0.76–1.70)	43	0.80 (0.56–1.15)	21.8	45	1.03 (0.66–1.61)	58	0.90 (0.61–1.32)
p for trend			1.0		0.07			1.0		0.39

[1] Localized disease was defined as Dukes A or B.

[2] Advanced disease was defined as Dukes C or D.

[3] All HRs and 95% confidence intervals (CIs) were adjusted for age at interview (yr), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), diabetes at baseline (no, yes), smoking history (never, "heavy" or ≥13 cigarettes per day starting age <15 years, "light" or nonheavy smokers), body mass index (<20, 20–23.9, 24–27.9, ≥28 m/kg^2), alcohol intake (0, <7, ≥7 drinks/week), education (no formal education, primary school, secondary school or higher), any weekly physical activity (no, yes), first degree relative diagnosed with colorectal cancer (no, yes), and total daily energy intake (kcal). CI = confidence interval.

[4] *p* for sex interaction among subjects with localized disease = 0.04.

[5] *p* for difference in relative risk for the localized *versus* the advanced colorectal cancer among women = 0.03.

[6] Monounsaturated fatty acids = MUFA.

TABLE III

HAZARD RATIOS (HR) FOR QUARTILES OF POLYUNSATURATED FATTY ACIDS (PUFAs) IN RELATION TO STAGE OF COLORECTAL CANCER AMONG THE ENTIRE COHORT

	Localized[1]			Advanced[2]		
	Cases, n	HR (95% CI)[3]	*p* for trend	Cases, n	HR (95% CI)[3]	p for trend
Total PUFA[4]						
3.2[4]	105	1.0 (Ref)		147	1.0 (Ref)	
4.3	90	0.96 (0.72–1.27)		130	0.98 (0.77–1.24)	
5.3	98	1.09 (0.82–1.44)		135	1.06 (0.84–1.34)	
7.3	83	0.94 (0.70–1.26)	0.93	115	0.91 (0.71–1.17)	0.66
Total n-3 PUFA						
0.36[4]	93	1.0 (Ref)		147	1.0 (Ref)	
0.45	109	1.29 (0.98–1.71)		118	0.88 (0.69–1.13)	
0.53	99	1.23 (0.92–1.63)		130	1.02 (0.80–1.29)	
0.67	75	0.97 (0.71–1.32)	0.85	132	1.07 (0.84–1.36)	0.42
Marine n-3 PUFA						
0.09[4]	93	1.0 (Ref)		121	1.0 (Ref)	
0.15	98	1.08 (0.82–1.44)		122	1.04 (0.81–1.33)	
0.21	95	1.07 (0.80–1.42)		132	1.14 (0.89–1.46)	
0.29	90	1.02 (0.76–1.37)	0.90[5]	152	1.33 (1.05–1.70)	0.01[5]
n-6 PUFA						
2.8[4]	107	1.0 (Ref)		149	1.0 (Ref)	
3.7	83	0.86 (0.65–1.15)		126	0.93 (0.73–1.18)	
4.7	103	1.12 (0.85–1.48)		136	1.05 (0.83–1.33)	
6.6	83	0.92 (0.68–1.23)	0.99	116	0.90 (0.70–1.16)	0.66
Total n-3/n-6 PUFA						
0.08[4]	92	1.0 (Ref)		117	1.0 (Ref)	
0.11	107	1.19 (0.90–1.57)		133	1.16 (0.91–1.49)	
0.13	94	1.06 (0.79–1.41)		130	1.16 (0.90–1.49)	
0.16	83	0.88 (0.65–1.19)	0.30	147	1.24 (0.97–1.59)	0.11
Marine n-3/n-6 PUFA						
0.02[4]	94	1.0 (Ref)		100	1.0 (Ref)	

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	Localized[1]			Advanced[2]		
	Cases, n	HR (95% CI)[3]	*p* for trend	Cases, n	HR (95% CI)[3]	p for trend
0.03	93	0.96 (0.72, 1.28)		139	1.36 (1.05, 1.76)	
0.05	92	0.95 (0.71, 1.27)		137	1.35 (1.04, 1.74)	
0.07	97	0.98 (0.73, 1.30)	0.85	151	1.45 (1.12, 1.87)	0.01

[1] Localized disease was defined as Dukes A or B.

[2] Advanced disease was defined as Dukes C or D.

[3] All HRs were adjusted for age at interview (yr), sex, dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), diabetes at baseline (no, yes), smoking history (never, “heavy” or ≥13 cigarettes per day starting age <15 years, “light” or nonheavy smokers), body mass index (<20, 20–23.9, 24–27.9, ≥28 m/kg^2), alcohol intake (0, <7, ≥7 drinks/week), education (no formal education, primary school, secondary school or higher), any weekly physical activity (no, yes), first degree relative diagnosed with colorectal cancer (no, yes), and total daily energy intake (kcal). CI = confidence interval.

[4] Median quartile values (g/1000 kcal).

[5] *p* for difference in relative risk for the localized *versus* the advanced colorectal cancer = 0.09.

TABLE IV

HAZARD RATIO (HR) FOR QUARTILES OF DIETARY POLYUNSATURATED FATTY ACIDS (PUFAs) IN RELATION TO COLORECTAL CANCER BY STAGE OF DISEASE, AMONG MEN AND WOMEN

	Men					Women				
	Median value (g/1000 kcal)	Localized[1]		Advanced[2]		Median value (g/1000 kcal)	Localized[1]		Advanced[2]	
		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]
Total PUFA										
Q1	3.2	66	1.0 (Ref)	95	1.0 (Ref)	3.3	39	1.0 (Ref)	52	1.0 (Ref)
Q2	4.2	52	0.94 (0.65–1.36)	66	0.82 (0.60–1.13)	4.3	38	0.97 (0.62–1.52)	64	1.23 (0.85–1.78)
Q3	5.3	49	0.97 (0.66–1.40)	73	0.99 (0.72–1.34)	5.3	49	1.24 (0.81–1.90)	62	1.20 (0.83–1.75)
Q4	7.2	43	0.97 (0.65–1.44)	57	0.86 (0.61–1.20)	7.4	40	0.91 (0.58–1.43)	58	1.03 (0.70–1.51)
p for trend			0.89		0.58			0.97		0.95
Total n-3 PUFA										
Q1	0.35	62	1.0 (Ref)	97	1.0 (Ref)	0.36	31	1.0 (Ref)	50	1.0 (Ref)
Q2	0.45	64	1.27 (0.89–1.80)	65	0.82 (0.60–1.12)	0.46	45	1.35 (0.86–2.14)	53	1.00 (0.68–1.47)
Q3	0.53	53	1.17 (0.81–1.70)	61	0.87 (0.63–1.20)	0.53	46	1.31 (0.83–2.08)	69	1.24 (0.86–1.79)
Q4	0.66	31	0.78 (0.51–1.21)	68	1.09 (0.80–1.50)	0.67	44	1.19 (0.75–1.89)	64	1.09 (0.75–1.59)
p for trend			0.41		0.67			0.59		0.43
Marine n-3 PUFA										
Q1	0.09	47	1.0 (Ref)	77	1.0 (Ref)[4]	0.09	46	1.0 (Ref)	44	1.0 (Ref)[4]
Q2	0.15	61	1.37 (0.94–2.01)	66	0.89 (0.64–1.24)	0.15	37	0.79 (0.51–1.21)	56	1.27 (0.86–1.89)
Q3	0.21	50	1.21 (0.81–1.80)	69	1.00 (0.72–1.38)	0.21	45	0.90 (0.60–1.36)	63	1.37 (0.93–2.01)
Q4	0.29	52	1.40 (0.94–2.08)	79	1.27 (0.93–1.75)	0.29	38	0.70 (0.45–1.07)	73	1.46 (1.00–2.12)
p for trend			0.17		0.11			0.17		0.05
n-6 PUFA										
Q1	2.8	67	1.0 (Ref)	95	1.0 (Ref)	2.9	40	1.0 (Ref)	54	1.0 (Ref)
Q2	3.7	49	0.87 (0.60–1.26)	67	0.84 (0.61–1.14)	3.8	34	0.85 (0.53–1.34)	59	1.09 (0.75–1.57)
Q3	4.7	52	1.01 (0.70–1.46)	72	0.97 (0.71–1.32)	4.7	51	1.26 (0.83–1.91)	64	1.19 (0.82–1.71)
Q4	6.5	42	0.92 (0.62–1.37)	57	0.85 (0.61–1.19)	6.7	41	0.91 (0.58–1.42)	59	1.01 (0.69–1.47)
p for trend			0.86		0.50			0.87		0.87
Total n-3/n-6 PUFA										
Q1	0.08	48	1.0 (Ref)	62	1.0 (Ref)	0.08	44	1.0 (Ref)	55	1.0 (Ref)

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	Men					Women				
	Median value (g/1000 kcal)	Localized[1]		Advanced[2]		Median value (g/1000 kcal)	Localized[1]		Advanced[2]	
		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]		Cases, *N*	HR (95% CI)[3]	Cases, *N*	HR (95% CI)[3]
Q2	0.11	61	1.21 (0.83–1.77)	77	1.20 (0.86–1.68)	0.11	46	1.17 (0.77–1.77)	56	1.11 (0.77–1.62)
Q3	0.13	55	1.13 (0.76–1.66)	71	1.15 (0.82–1.62)	0.13	39	0.98 (0.64–1.52)	59	1.15 (0.80–1.67)
Q4	0.16	46	0.93 (0.62–1.41)	81	1.32 (0.94–1.84)	0.16	37	0.82 (0.53–1.28)	66	1.15 (0.80–1.65)
p for trend			0.66		0.15			0.29		0.44
Marine n-3/n-6 PUFA[5]										
Q1	0.02	49	1.0 (Ref)	55	1.0 (Ref)[5]	0.02	45	1.0 (Ref)	45	1.0 (Ref)[5]
Q2	0.03	51	0.97 (0.66, 1.44)	88	1.48 (1.06, 2.07)	0.03	42	0.95 (0.63, 1.45)	51	1.18 (0.79, 1.76)
Q3	0.05	54	1.06 (0.72, 1.56)	59	1.03 (0.71, 1.49)	0.05	38	0.83 (0.53, 1.27)	78	1.72 (1.19, 2.49)
Q4	0.07	56	1.08 (0.73, 1.59)	89	1.54 (1.09, 2.16)	0.07	41	0.86 (0.56, 1.32)	62	1.32 (0.90, 1.95)
p for trend			0.610		0.095			0.383		0.052

[1] Localized disease was defined as Dukes A or B.

[2] Advanced disease was defined as Dukes C or D.

[3] All HRs and 95% confidence intervals (CIs) were adjusted for age at interview (yr), dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), diabetes at baseline (no, yes), smoking history (never, "heavy" or ≥13 cigarettes per day starting age <15 years, "light" or nonheavy smokers), body mass index (<20, 20–23.9, 24–27.9, ≥28 m/kg^2), alcohol intake (0, <7, ≥7 drinks/week), education (no formal education, primary school, secondary school or higher), any weekly physical activity (no, yes), first degree relative diagnosed with colorectal cancer (no, yes), and total daily energy intake (kcal). CI = confidence interval.

[4] *p* for interaction by sex = 0.80.

[5] *p* for interaction by sex = 1.0.

TABLE V

HAZARD RATIOS (HR) FOR QUARTILES OF MARINE n-3 POLYUNSATURATED FATTY ACIDS[1] IN RELATION TO STAGE OF COLORECTAL CANCER BY DURATION OF FOLLOW-UP AMONG THE ENTIRE COHORT

	≤5 years			5–10 years			>10 years		
	Cases, n	**HR (95% CI)[2]**	**p for trend**	**Cases, n**	**HR (95% CI)[2]**	**p for trend**	**Cases, n**	**HR (95% CI)[2]**	***p* for trend**
Overall									
0.09[3]	84	1.0 (Ref)		107	1.0 (Ref)		36	1.0 (Ref)	
0.15	90	1.12 (0.83–1.51)		116	1.12 (0.86–1.45)		26	0.69 (0.42–1.15)	
0.21	95	1.22 (0.91–1.63)		99	0.98 (0.74–1.28)		47	1.22 (0.79–1.89)	
0.29	106	1.35 (1.01–1.80)	0.04[4]	127	1.27 (0.98–1.65)	0.15[4]	28	0.77 (0.47–1.26)	0.85[4]
Localized disease[5]									
0.09[3]	37	1.0 (Ref)		40	1.0 (Ref)		16	1.0 (Ref)	
0.15	41	1.18 (0.75–1.84)		46	1.19 (0.78–1.83)		11	0.64 (0.30–1.38)	
0.21	38	1.12 (0.71–1.76)		36	0.96 (0.61–1.51)		21	1.16 (0.61–2.23)	
0.29	39	1.15 (0.73–1.81)	0.61	40	1.10 (0.70–1.70)	0.93	11	0.62 (0.29–1.34)	0.55
Advanced disease[6]									
0.09[3]	43	1.0 (Ref)		63	1.0 (Ref)		15	1.0 (Ref)	
0.15	47	1.14 (0.75–1.72)		62	1.01 (0.71–1.43)		13	0.85 (0.41–1.79)	
0.21	53	1.32 (0.88–1.97)		54	0.90 (0.62–1.29)		25	1.64 (0.86–3.11)	
0.29	60	1.49 (1.00–2.21)	0.04[7]	78	1.32 (0.94–1.84)	0.17[7]	14	0.98 (0.47–2.04)	0.53[7]

[1] All nutrient values were energy adjusted.

[2] All HRs were adjusted for age at interview (yr), sex, dialect group (Cantonese, Hokkien), interview year (1993–1995, 1996–1998), diabetes at baseline (no, yes), smoking history (never, "heavy" or ≥13 cigarettes per day starting age <15 years, "light" or nonheavy smokers), body mass index (<20, 20–23.9, 24–27.9, ≥28 m/kg^2), alcohol intake (0, <7, ≥7 drinks/week), education (no formal education, primary school, secondary school or higher), any weekly physical activity (no, yes), first degree relative diagnosed with colorectal cancer (no, yes), and total daily energy intake (kcal). CI = confidence interval.

[3] Median values (g/1000 kcal) for quartile of marine n-3 PUFA intake.

[4] *p* for difference in relative risk for colorectal cancer at follow-up ≤5 years *versus* 5–10 years *versus* >10 years among the entire cohort = 0.17.

[5] Localized disease was defined as Dukes A or B.

[6] Advanced disease was defined as Dukes C or D.

[7] p for difference in relative risk for colorectal cancer at follow-up ≤5 years *versus* 5–10 years *versus* >10 years among subjects with advanced disease = 0.36.