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Dietary fatty acids, luminal modifiers, and risk of colorectal cancer

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Abstract

Inconsistent observations in epidemiologic studies on the association between total fat intake and colorectal cancer may be ascribed to opposing effects of individual fatty acids and the presence of other dietary constituents that modify luminal or systemic lipid exposure. We analyzed the data from a population-based case-control study that included 1163 cases and 1501 controls to examine the effects of individual fatty acid groups on colorectal cancer risk as well as their interactions with calcium and fiber intake. Odds ratios (OR) and 95% confidence intervals (CI) were estimated by unconditional logistic regression model according to quartile levels of energy-adjusted fatty acid intake. In the bivariable analyses, the risk of colorectal cancer increased with trans fatty acid (TFA) intake (OR for top vs bottom quartile =1.46, 95% CI 1.17-1.59, p-value for a trend <0.001), but the associations was substantially attenuated in multivariable analyses (p-value for a trend =0.176). However, a significant linear trend in the multivariable OR (p=0.029) for TFA was present for subjects with lower calcium intake. Furthermore, multivariable ORs progressively decreased with increasing both omega-3 and omega-6 polyunsaturated fatty acid intake (P-values for linear trend: 0.033 and 0.011, respectively) for subjects with lower dietary fiber intake. These interactions were also significant or marginally significant (P = 0.085 for TFA, 0.029 for omega-3 and 0.068 for omega-6). Our results suggest that populations with lower intake of luminal modifiers, i.e., calcium and fiber, may have differential risks of colorectal cancer associated with dietary fatty acid intake.

Keywords

Fatty acids; colorectal cancer; case-control study; calcium; fiber

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Introduction

Collective evidence from analytic epidemiological studies and clinical trials does not support the relationship between total fat intake and colorectal cancer,[1-3] despite unequivocal data in experimental animals and several plausible biological mechanisms.[4-6] The discrepancy may be ascribed to several factors, including limitations in dietary measurements, genetic susceptibilities to fat-induced genotoxic or metabolic effects, and heterogenous composition of dietary fat. Indeed, dietary fats (triglycerides) consists of several groups of fatty acids that are chemically classified by length of the carbon chain (long, medium and short) as well as by the number (saturated (SFA), mono-unsaturated (MUFA) or poly-unsaturated (PUFA)), position (omega-3 and omega-6), sequence (conjugated) and configuration (cis or trans) of double bonds.[5,6] Some of these fatty acids, such as omega-3 PUFA, MUFA, and conjugated linoleic acid, may exert cancer preventive effects, while others, such as SFA, omega-6 PUFA and trans fatty acids (TFA), may increase the risk of colorectal cancer.[1,6] Consequently, opposing effects of these individual fatty acids may lead to the overall null association between total fat intake and colorectal cancer.

Various dietary components also interfere with intestinal lipid metabolism and thus may modify the effect of dietary fatty acids. Dietary calcium has been postulated to protect against colorectal cancer,[7] because calcium binds cytotoxic secondary bile acids and fatty acids to form insoluble soaps in the bowel lumen.[8-9] Dietary fiber which provides substrates for bacterial fermentation to produce anti-carcinogenic agents, e.g., short chain fatty acids,[1] is known to slow intestinal lipid absorption and reduce circulating cholesterol levels in mildly hypercholesterolemic patients.[10-11] In this population-based case-control study, we aimed to address whether specific dietary fatty acids affect the risk of colorectal cancer in conjunction with dietary calcium and fiber.

Materials and methods

Study procedures

The study has been approved by Wayne State University Human Investigation Committee and all subjects gave written informed consent to participate in the study. This original study "Luminal lipid exposure, genetics and colon cancer risk" was designed to address the hypothesis that intracolonic exposure to potentially carcinogenic lipid metabolites may increase the risk of colorectal cancer. Details concerning the ascertainment, recruitment and characteristics of the study subjects have been described elsewhere [submitted for publication]. In brief, eligible study subjects were residents in the Metropolitan Detroit Tri-County (Wayne, Oakland and Macomb) area, between 45 and 80 years of age at time of ascertainment, with a working telephone and no prior history of any invasive cancer, in-situ colorectal cancer or colectomy. Eligible colorectal cancer cases were histologically diagnosed between January 1, 2003 and September 30, 2005, and were identified through the Metropolitan Detroit Cancer Surveillance System, and frequency-matched population controls through random digit dialing. A total of 1,335 cases (41.7%) and 1,682 controls (59.4%) consented to the study, and 1,205 cases and 1,547 controls of these remained to be eligible after completion of the study. The cases and controls were well balanced concerning the matching variables, age, race and county of residence, but gender-matching was incomplete (50% and 57% females in the cases and controls, respectively). More, specifically, the median age at diagnosis/identification was 62 and 63 years for the cases and controls, 26.2% and 26.5% were African Americans, 70% and 69% Caucasians, and the rest other racial groups in the cases and controls, while 20.9% and 20.5% were current cigarettes smokers in these respective groups. In addition, the cases included less college graduates

than the controls (22% vs. 32%), reported more frequently family history of colorectal cancer (14% vs 10%), and less often chose blood as a biospecimen (66% vs. 71%).

The subjects were interviewed over the telephone using structured questionnaires regarding their usual diet and other risk factors for colorectal cancer for the time-period preceding cancer diagnosis (approximately 2 years prior to the interview). Specifically, a validated semi-quantitative food frequency questionnaire (FFQ), Block 98.2 (Block Dietary Data Systems, Berkeley, CA), was used to estimate daily nutrient (including individual fatty acid groups) intake. This questionnaire has been validated against multiple diet records where the correlation coefficients for total fat, SFA, MFA and PUFA have been reported to be 0.58-0.60, 0.58-0.63, 0.56-0.59, 0.44-0.48, respectively,12¯13 and chosen based on its superiority to categorize individuals on energy from fat14 as compared to the Willett instrument as dietary fat was a main focus of the study. Omega-6 PUFA intake was obtained by subtracting the sum of omega-3 PUFA, cis-MUFA, TFA and SFA intake from total fat intake. The data for specific omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), were not available from this questionnaire. Total calcium and other vitamin/mineral intake was computed as the sum of energy-adjusted dietary intake and intake from supplements.

Statistical analysis

The residual method described by Willett and Stampfer15 was chosen as the primary strategy for energy adjustment based on the report that it was more powerful for detecting trends in relative odds.16 However, we also explored the energy-density model using percent calories from individual fatty acids and the energy substitution model (in expense of carbohydrate) including total calorie intake, energy-adjusted total protein and individual fatty acids intake simultaneously17 to see if the results were equivalent. First, the differences in median intake of selected nutritional variables of the cases and controls were tested by the Wilcoxon rank-sum test. Odds ratios (ORs) and 95% confidence intervals (CIs) for colorectal cancer associated with dietary fatty acid intake were estimated using an unconditional logistic regression model,18 adjusting for selected covariates as described below. Dietary fat intake was grouped into quartiles based on distributions of the cases and controls combined in these analyses and the lowest quartile was used as the reference category to calculate ORs. Tests for linear trend in the logit of risk associated with ordinal dietary intake were performed using median intake of each quartile.

Because of the unbalanced gender matching, we first calculated bi-variable (gender-adjusted) ORs, instead of univariable ORs. Then, additional covariates were first selected from established risk factors for colorectal cancer in the literature.1،19،20 They were tested one at a time in a model that included basic demographic variables, age, gender and educational levels, and those showing an association at the 10% level were included to estimate multivariable ORs along with the type of biospecimens provided (blood vs. others) as a potential factor for selection bias. As a result, the final multivariable model included age, gender, educational level, biospecimen type, total calcium, fiber, family history of colorectal cancer, regular (>= 3 times per week for 6 months or longer) non-steroidal anti-inflammatory drug (NSAID) use, body mass index (body weight (kg)/body height $(m)^2$), and physical activity index in their 30s, which was the weighted sum of time the subject spent per 24 hours as described previously,21 pack-years of cigarette smoking and postmenopausal hormone replacement therapy (in women). The last two variables were forced to be included in the model given the evidence from the literature.19،20 Vitamin D, dietary heme, alcoholic drinks, race and height were also assessed and were not included in the final model (P>0.10). Major dietary sources of fatty acids, such as red meat, were not included in the model simultaneously because their inclusions (i.e., controlling their intake levels) alter the interpretation of regression coefficients for individual fatty acids. After

exclusion of subjects with missing covariates, the final analytical samples in this study consisted of 1163 cases ands 1501 controls. In addition, the ORs associated with dietary fatty acid intake were calculated, stratified by total calcium and fiber intake level at medians in the entire study population, where these stratification variables were excluded from respective multivariable models. The interactions between ordinal dietary fatty acid intake and a dichotomized stratification variable were tested by the inclusion of multiplicative interaction terms between these variables. Dietary predictors for individual fatty acids and dietary fiber and calcium intake were assessed by means of Spearman correlation coefficients. All statistical analyses were performed using SAS version 9.

Results

Nutritional profiles (median and quartile levels) of the total study population as well as the cases and controls are presented in Table I. Overall, median total energy intake was 2040 kcal per day, 37.4% of which was contributed by dietary fat. Median total fat intake was 96 g per day, which was primarily divided into MUFA (36.3g), SFA (28.7g), omega-6 PUFA (20.2), whereas TFA (7.7g) and omega-3 PUFA (2.0g) intakes were much lower. The cases were more obese, and consumed more calories and TFA and less omega-3 PUFA, fiber and calcium. Although total calorie intake was higher in males (2515 kcal) than in females (2055 kcal), percent energy from fat and energy adjusted fat intake were almost identical in both genders (37.8% vs 37.3% and 96.0 and 96.9 g, respectively). Major dietary predictors of individual fatty acids and dietary fiber and calcium intake in this population were cheese and red meat for SFA, nuts and red meat for cis-MUFA, nuts and mayonnaise for omega-6 PUFA, fish and poultry for omega-3 PUFA, margarine and cake for trans fat, vegetables and beans for dietary fiber and dairy and supplements for calcium.

In the bi-variable models, significantly increased ORs were observed for the 2nd and 3rd quartiles of SFA (OR1=1.26, 95% CI 1.02-1.57) and for the highest quartile of TFA (OR1 =1.46, 95% CI 1.17-1.59, p-value for a linear trend <0.001), while the risk of colorectal cancer tended to progressively decreased with omega-6 PUFA intake (P =0.068). When other covariates were considered (OR2), none of these associations remained statistically significant (Table II), except a marginal trend left for omega-6 PUFA.

Energy density models based percent calories from individual fats generally yielded similar results, but the associations tended to be slightly weakened for total and major fatty acids while they were slightly pronounced for minor fatty acids. The ORs for the top versus bottom quartile and p-values for linear trend (in parentheses) were as follows; 0.96 (95% CI 0.76-1.21) (p=0.972), 0.99 (95% CI 0.78-1.25) (p=0.948),1.00 (95% CI 0.79-1.25) (p=0.977), 0.81 (95% CI =0.65-1.02) (p=0.056), 0.88 (95% CI 0.70-1.10) (p=0.226), and 1.22 (0.97-1.53) (p=0.046) for total fat, SFA, cis-MUFA, omega-6, omega-3, and TFA, respectively. We also attempted simultaneous adjustment for all fatty acids in the multivariable residual model as well as in the substitution model in expense of carbohydrate with energy adjusted intakes, which produced almost identical results with differences of up to 0.02 in the ORs. The ORs for the top versus bottom quartile in non-substitution simultaneous adjustment model were 0.99 (95% CI 0.74-1.33), 0.98 (95% CI 0.72-1.32), 0.84 (95% CI 0.63-1.11) and 1.17 (95% CI 0.92-1.51) for SFA, cis-MUFA, omega-6 PUFA and TFA, respectively, while the association with omega-3 was slightly insignificantly reduced with the OR approaching unity, 1.03 (95% CI 0.79-1.33).

In the stratified analyses by calcium intake (Table III), we found that the multivariable ORs progressively increased with TFA intake (P-value for a linear trend =0.029) when calcium intake was lower than the median (900 mg per day) and there was a marginally significant interaction between calcium and TFA (P=0.085). There were no such interactions between

calcium and other groups of fatty acids. In the stratified analyses by dietary fiber (Table IV), we found the multivariable ORs progressively decreased with increasing both omega-3 and omega-6 PUFA intake (P-values for linear trend: 0.031 and 0.011, respectively) among subjects with fiber intake lower than median (18.6 g per day). The ORs for the top versus bottom quartiles were 0.72 (95% CI 0.53-1.00) and 0.69 (95% CI: 0.50-0.95), respectively, and their interactions were also significant for omega-3 (P=0.029) and marginally significant for omega-6 fatty acid (P=0.068).

In order to address differences between non-marine omega-3 PUFAs (primarily alpha-linolenic acid (ALA)) and highly unsaturated marine PUFAs, e.g., DHA and EPA, we fitted separate multi-variable models including total fish intake and omega-3 PUFAs simultaneously and assessed the potential effects of non-marine omega-3 PUFA. These models revealed that the ORs associated with the top versus bottom quartile of omega-3 PUFA intake and the p-values for linear trend did not differ significantly from those presented in Tables II and IV, OR= 0.90 (95% CI .072-1.13) and p= 0.322 for the overall subjects and OR=0.73 (95% CI 0.53-1.01) and p= 0.044 for the subjects with lower fiber intake, suggesting equivalent associations with both classes of omega-3 PUFAs.

Additional stratified analyses were also performed to confirm previously reported differential associations by other co-factors, namely gender and NSAID use.22,23 The gender-stratified analyses did not find differential effects of TFA with the ORs for the top versus bottom quartile of 1.23 (95% CI 0.88-1.71) for males, 1.09 (0.78-1.51) for females. When 1,928 non-NSAID users and 736 NSAID users were analyzed separately, the ORs associated with the top versus bottom quartile intake of omega-3 PUFA and TFA were comparable, although they tended to be more pronounced in non-users, i.e., 0.89 (95% CI 0.69-1.16) vs.1.03 (95% CI 0.66-1.62) in non-users and users, respectively, for omega-3 and 1.19 (95% CI 0.91-1.55) vs.1.08 (95% CI 0.68-1.75), respectively, for TFA. Their interactions were not significant (p=0.443 and p= 0.889, respectively).

Discussion

The overall null associations with total fat and individual dietary fatty acids found in the present study are consistent with results from other prospective cohort and population-based case-control studies. Furthermore, two large clinical trials, Polyp Prevention Trial and Women's Health Initiative, have failed to demonstrate that reducing calories from total fat to 20% of energy helps decrease the recurrence of colorectal adenoma or the incidence of colorectal cancer.3,24 However, our results suggest that populations with lower intake of luminal modifiers, i.e., calcium and fiber, may have differential risks of colorectal cancer associated with dietary fatty acid intake. To our knowledge, this is the first to report such interactions between individual dietary fatty acid intake and calcium or fiber. These analyses were a priori defined as part of an investigation on luminal lipid exposure and colorectal cancer risk and not a posteriori analyses because of null findings on the main effects. The interactions between total fat and calcium intake were examined in a few studies, yielding contradictory results. Whereas Martínez et al found that the risk of colorectal adenoma associated with high fat intake was more pronounced with lower calcium intake,25 De Stefani et al found that the risk of colorectal cancer associated with high fat intake was more pronounced in the subjects with higher calcium intake.26

One of the significant findings in this study was the increased risk associated with high TFA intake, in conjunction with low calcium intake. TFAs are unsaturated fatty acids with at least one double bond in the trans configuration, are largely consumed from industrially produced partially hydrogenated vegetable oils found in commercial bakery products, deep fried foods and packaged snacks.27 TFA has unfavorably affect blood lipid contents, elicit systemic

inflammation, induce endothelial dysfunction and promote insulin resistance,28 which may also influence the risk of colorectal cancer. Yet, information concerning the effects on cancer have thus far been limited, with only a few showing a positive association with dietary intake.29 As noticed in this study, an appreciable attenuation in the association with colorectal cancer/adenoma after adjustment of other covariates has also been reported,22،30،31 probably due to their relatively distinguished dietary sources which are likely closely correlated with other life style factors. Although none of earlier studies examined calcium as an effect modifier, there are plausible biological bases. Calcium soaps of long-chain fatty acids are present in human feces32 and calcium binding are stronger for mono than polyunsaturated fatty acids, similarly to SFA33 and predominant forms of industrial hydrogenated TFAs belong to MUFA.29 Because the chemical structure of TFAs resembles that of SFAs, they also share similar chemical/physical properties34 and thus a trans-isomer of MUFA has stronger calcium affinity than the corresponding cis-isomer.35 Accordingly, the presence of a sufficient amount of unabsorbed calcium in the intestinal lumen may offset the detrimental effects of TFAs. In this respect, it is interesting to note that naturally occurring (dairy) TFAs with high calcium content have less unfavorable metabolic effects.36-37 This also suggests that calcium fortification may be an possible option for commercial baked goods where TFA replacement is not practical.

The data from the present study also suggest that both omega-3 and -6 may reduce the risk of colorectal cancer in a certain group of the subjects. Omega-3 PUFAs have been postulated to exert anti-carcinogenic effects through several mechanisms.38 These include the modulation of arachidonic acid-derived prostaglandin synthesis, immuno-inflammatory pathways and *Ras* oncogene and protein kinase C activities, which ultimately lead to decreases in epithelial cell proliferation and angiogenesis, and increases in apoptosis and cell differentiation.39 Among omega-3 PUFAs, highly unsaturated longer chain marine fatty acids, EPA and DHA, are generally more potent and more bioavailable than non-marine ALA, suggesting possible differential effects of these PUFAs.40-42 On the other hand, omega-6 PUFAs may have a detrimental effect as they interfere with the potential beneficial effects of omega-3 in the same metabolic pathways43 and synthesize more pro-inflammatory than aniti-inflammatory molecules.44 Corroboratively, tumor promoting effect has been reported in some animal and in vitro models.6

Despite these plausible biological mechanisms and persuasive evidence from animal and in vitro models, to date the data from epidemiologic studies and clinical trials do not support the associations between either group of PUFA and cancer in general or colorectal cancer. Protective effects of omega-3 PUFA on total cancer incidence/mortality have not seen in secondary analysis of randomized clinical trial primarily targeted for cardiovascular diseases (CVD).45 In the meta-analysis of prospective cohort studies, the summary relative risks (RR) of colorectal cancer was 0.91 (95% CI: 0.70-1.19) for the comparison between the highest versus lowest omega-3 PUFA intake and 0.88 (95% 0.78-1.00) for fish intake as a surrogate.46 However, recent results from a long-term cohort study in the US and case-control studies in Scotland and among French-Canadians showed a progressive decline in risk of colorectal cancer with increasing omega-3 PUFA intake.31،47-48

The association between omega-6 PUFA or its primary source, linoleic acid (LA), and colorectal cancer has been equally equivocal. There in no evidence from the secondary analyses of clinical trials for CVD that omega-6 PUFAs increase the incidence of cancer in general.49 The meta-analysis of epidemiologic studies indicates the summary risk estimate for colorectal or colon cancer is less than unity (OR=0.92, 95% CI 0.85-1.08, RR= 0.92, 95% CI 0.70-1.22).49 While a case-control study for colorectal adenoma based on serum fatty acid levels found a strong positive association with omega-6 PUFA,50 a nested case-

control study for colorectal cancer based on erythrocyte fatty acid contents revealed a strong inverse association.51

Because dietary fiber inhibit intestinal lipid absorption,10-11 higher intake of dietary fiber may offset potential beneficial effects commonly shared by the both groups of PUFAs,44 such as effects on insulin sensitivity and oxidative stress. In this context, it is interesting to note that a low frequency of colon cancer in fishing communities of South Africa has been attributed to high omega-3 PUFA intake and low dietary fiber intake.52 Nonetheless, because dietary fiber was found to have a stronger protective effect overall in the present study (OR for the top vs bottom quartile: 0.59, 95% CI: 0.47-0.75, p-value for trend <0.001, data not shown) than these PUFAs, increasing dietary fiber intake appears to be a better strategy for colorectal cancer prevention.

We acknowledge several limitations in this study. Due to the relative low participation rate, self-selection bias or volunteer bias is a concern.53 In fact, higher proportions of college graduates and of those who chose to donate blood in the control group were indicative of this bias. Thus, we adjusted for these factors and others in calculating multivariable ORs and in fact the multivariable ORs differed considerably from the bi-variate ORs for some estimates. Yet, it is possible that residual unmeasured factors may have been confounded with the observed associations. Differential recalls between the cases and controls (recall bias) is also a concern in any retrospective studies like this study. Cases who are aware of their own diagnosis may recall past exposures differently from controls. But the use of structured questionnaires (like our study) has been shown to reduce this bias54 and the median numbers of food items consumed per day with this FFQ were very similar between the cases and the controls (8.99 vs 9.13, P=0.630). There is significant likelihood that some of the associations observed in this study were chance findings due to multiple comparisons, although these stratified analyses were selected a priori for their potentials to modify luminal or systemic fat exposure. Furthermore, investigators have recently recognized that the estimated intakes from FFQs, such as the one used in this study, are subject to substantial error that can profoundly attenuate diet-disease associations.55 Thus, the overall null associations in the present study are possibly due to insufficient statistical power, in view of the attenuation of the associations from measurement errors. The FFQ version we used adapted 11 supplemental questions to take low-fat dietary habits into account, which have been demonstrated to result in higher precision of the estimates.56 This version also collected additional detail on types of fat used in cooking, which has been validated for the assessment for dietary TFA.57 However, we acknowledge that the Block 98.2 is arguably not the best instrument for fatty acid intake without validation for a group of fatty acids, including trans fat, omega-3 and omega-6. Besides, no estimates for individual omega-3 PUFAs, e.g., DHA and EPA, limited the interpretation of our results.

Despite the limitations discussed above, higher total fat (including TFA) intake in our study population, compared with other population samples or study participants in similar age groups,58-59 was considered to be advantageous in assessing its association. Overall, the results of present study suggest that (1) luminal lipid modifiers may modify the association of dietary fat with colorectal cancer, and (2) the association between dietary fat and colorectal cancer, if any, is more likely through systemic or metabolic rather than luminal. The former may partially explain the inconsistencies that have been observed in epidemiologic studies over time and across populations. Intake of total dietary fat indeed has been declining in the US for the past few decades while that of fiber and calcium been rather increasing,60-63 which may have attenuated the associations with dietary fat. Potential modest effect of TFA on risk of colorectal cancer also deserves further investigation.

The novelty and impact of the paper

Our results suggest that populations with lower intake of luminal modifiers, i.e., calcium and fiber, may have differential risks of colorectal cancer associated with dietary fatty acid intake. This may partially explain the inconsistent epidemiologic observations on the association between dietary fat and colorectal cancer over time and across populations.

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Table I

Nutritional profile of the study population

		Overall (N=2664)		Cases (N=1163)		Controls (N=1501)		
Nutritional characteristics	**Unit**	**Median**	**(Quartile range)**	**Median**	**(Quartile range)**	**Median**	**(Quartile range)**	**P-values**
Total energy	Kcal/day	2040	(1581 - 2691)	2085	(1606 - 2801)	2023	(1563 - 2618)	0.004
Protein energy	%	14.8	(13.0 - 16.9)	14.6	(12.7 - 16.7)	15.0	(13.2 - 17.0)	0.002
Carbohydrate energy	%	47.8	(42.3 - 53.1)	47.6	(42.4 - 52.6)	48.0	(42.2 - 53.4)	0.306
Fat energy	%	37.4	(32.8 - 42.1)	37.8	(33.2 - 42.0)	37.1	(32.3 - 42.4)	0.184
Energy-adjusted intake								
Total fat	g/day	96.05	(86.21 - 106.46)	96.54	(86.73 - 106.11)	95.59	(85.99 - 106.86)	0.583
Saturated fatty acids	g/day	28.66	(25.18 - 32.32)	28.75	(25.51 - 32.36)	28.61	(24.86 - 32.32)	0.200
cis-MUFA	g/day	36.31	(31.90 - 40.66)	36.17	(32.00 - 40.66)	36.33	(31.81 - 40.67)	0.517
Omega-6 PUFA	g/day	20.21	(16.68 - 24.42)	19.95	(16.30 - 24.31)	20.39	(16.91 - 24.60)	0.019
Omega-3 PUFA	g/day	1.97	(1.66 - 2.41)	1.96	(1.65 - 2.40)	1.98	(1.67 - 2.42)	0.503
Trans fatty acid	g/day	7.71	(6.13 - 9.24)	7.86	(6.27 - 9.62)	7.60	(6.04 - 9.04)	0.004
Calcium	mg/day	899.6	(688.5 - 1307.7)	858.1	(662.1 - 1164)	946.0	(711.7 - 1417)	<0.001
Fiber	g/day	18.59	(15.45 - 22.89)	18.02	(14.91 - 21.99)	19.03	(16.00 - 23.59)	<0.001
Alcohol	drinks/week	0.23	(0 - 3.74)	0.20	(0 - 4.06)	0.23	(0 - 3.55)	0.869
Body mass index	kg/m2	27.46	(24.43 - 31.54)	28.00	(24.90 - 31.93)	27.29	(24.39 - 31.2)	0.004

MUFA:Mono unsaturated fatty acids, PUFA: poly unsaturated fatty acids

P-vales for differences between the cases and controls based on the Wilcoxon rank-sum test

Table II

Bi-variable and multivariable odds ratios (OR) and 96% confidence intervals (CI) for colorectal cancer according to quartile levels of dietary fatty acid intake

Dietary fatty acids	No of cases/controls	OR1	95% CI	OR2	95% CI
Total fat	285/381	1.00	-	1.00	-
	280/386	1.00	(0.80-1.24)	0.89	(0.71-1.11)
	317/349	1.24	(1.00-1.55)	1.08	(0.86-1.36)
	281/385	0.99	(0.79-1.23)	0.84	(0.67-1.06)
		P=0.725		P=0.307	
Saturated fatty acids	267/399	1.00	-	1.00	-
	301/365	1.26	(1.02-1.57)	1.10	(0.88-1.38)
	303/363	1.26	(1.02-1.57)	1.03	(0.82-1.30)
	292/374	1.15	(0.92-1.43)	0.95	(0.75-1.21)
		P=0.246		P=0.583	
cis MUFA	281/385	1.00	-	1.00	-
	302/364	1.15	(0.92-1.43)	1.06	(0.84-1.32)
	290/376	1.07	(0.86-1.32)	0.91	(0.73-1.14)
	290/376	1.05	(0.84-1.30)	0.94	(0.74-1.18)
		P=0.829		P=0.391	
Omega-6 PUFA	322/344	1.00	-	1.00	-
	286/380	0.84	(0.68-1.04)	0.81	(0.65-1.02)
	272/394	0.77	(0.62-0.96)	0.75	(0.60-0.94)
	283/383	0.81	(0.66-1.01)	0.81	(0.65-1.02)
		P=0.068		P=0.088	
Omega-3 PUFA	296/370	1.00	-	1.00	-
	295/371	1.02	(0.82-1.27)	0.96	(0.77-1.20)
	287/379	0.97	(0.78-1.20)	0.90	(0.72-1.12)
	285/381	0.96	(0.77-1.19)	0.92	(0.73-1.15)
		P=0.609		P=0.414	
Trans fatty acids	271/395	1.00	-	1.00	-
	277/389	1.07	(0.83-1.34)	0.99	(0.79-1.25)

Dietary fatty acids	No of cases/controls	OR1	95% CI	OR2	95% CI
	289/377	1.17	(0.94-1.46)	0.99	(0.79-1.25)
	326/340	1.46	(1.17-1.59)	1.17	(0.93-1.48)
		P<0.001		P=0.176	

MUFA:Mono unsaturated fatty acids, PUFA: poly unsaturated fatty acids

OR11: adjusted for gender

OR2: adjusted for age, gender, specimen type (blood vs. others), total calcium and dietary fiber intake, physical activities in their 30s, body mass index, family history of colorectal cancer, pack-years of cigarette smoking and postmenopausal hormone use (women), highest education achieved and NSAID use.

P-values for a linear trend with the median intake of each quartile level

Table III

Multivariable odds ratios and 95% confidence intervals (CI) for colorectal cancer according to quartile levels of dietary fatty acid intake stratified by total calcium intake at median

	Below Median			Above median		
Dietary fatty acids	**No of cases/controls**	**OR**	**95% CI**	**No of cases/controls**	**OR**	**95% CI**
Total fat	123/131	1.00	-	162/250	1.00	-
(P=0.686)	147/166	0.92	(0.65-1.29)	133/220	0.89	(0.65-1.20)
	192/172	1.18	(0.85-1.64)	125/177	0.97	(0.71-1.34)
	175/226	0.80	(0.58-1.11)	106/159	0.92	(0.65-1.29)
		P=0.268			P=0.698	
Saturated fatty acids	143/152	1.00	-	124/247	1.00	-
(P=0.224)	171/181	0.94	(0.68-1.30)	130/184	1.27	(0.92-1.77)
	170/189	0.82	(0.60-1.14)	133/174	1.31	(0.94-1.84)
	153/173	0.80	(0.57-1.13)	139/201	1.10	(0.78-1.55)
		P=0.154			P=0.604	
cis MUFA	116/139	1.00	-	165/246	1.00	-
(P=0.810)	164/150	1.31	(0.93-1.84)	138/214	0.92	(0.68-1.25)
	174/190	1.08	(0.78-1.50)	116/186	0.78	(0.56-1.07)
	183/216	1.02	(0.74-1.41)	107/160	0.94	(0.68-1.32)
		P=0.668			P=0.504	
Omega-6 PUFA	151/128	1.00	-	171/216	1.00	-
(P=0.506)	154/168	0.82	(0.59-1.14)	132/212	0.82	(0.60-1.12)
	149/197	0.68	(0.49-0.94)	123/197	0.85	(0.62-1.16)
	183/202	0.86	(0.62-1.18)	100/181	0.74	(0.53-1.03)
		P=0.428			P=0.096	
Omega-3 PUFA	146/138	1.00	-	150/232	1.00	-
(P=0.337)	158/168	0.88	(0.63-1.22)	137/203	1.02	(0.75-1.40)
	171/188	0.87	(0.63-1.20)	116/191	0.89	(0.65-1.23)
	162/201	0.79	(0.58-1.09)	123/180	1.03	(0.75-1.42)
		P=0.176			P=0.972	
Trans fatty acids	121/156	1.00	-	150/239	1.00	-

	Below Median			Above median		
Dietary fatty acids	**No of cases/controls**	**OR**	**95% CI**	**No of cases/controls**	**OR**	**95% CI**
(P=0.085)	135/172	1.00	(0.71-1.41)	142/217	1.02	(0.75-1.38)
	161/176	1.15	(0.82-1.60)	128/201	0.89	(0.65-1.23)
	220/191	1.37	(0.99-1.88)	106/149	1.00	(0.70-1.39)
		P=0.029			P=0.773	

MUFA:Mono unsaturated fatty acids, PUFA: poly unsaturated fatty acids. Median = 899.6 g

OR: adjusted for age, gender, biospecimen type (blood vs. others), dietary fiber, physical activities in their 30s, body mass index, family history of colorectal cancer, pack-years of cigarette smoking and postmenopausal hormone use (women), highest education achieved, and NSAID use.

P-values following the last ORs for each fatty acid are for a linear trend with the median intake of quartiles of each fatty acid and p-values in the parentheses are for interaction with calcium

Table IV

Multivariable odds ratios and 95% confidence intervals (CI) for colorectal cancer according to quartile levels of dietary fatty acid intake stratified by dietary fiber intake at median

	Below Median			Above median		
Dietary fatty acids	**No of cases/controls**	**OR**	**95% CI**	**No of cases/controls**	**OR**	**95% CI**
Total fat	143/135	1.00	-	142/246	1.00	-
(P=0.200)	135/156	0.77	(0.55-1.08)	145/230	1.04	(0.77-1.41)
	179/178	0.95	(0.69-1.32)	138/171	1.28	(0.93-1.77)
	179/227	0.75	(0.55-1.03)	102/158	0.98	(0.70-1.39)
		P=0.158			P=0.745	
Saturated fatty acids	107/109	1.00	-	160/290	1.00	-
(P=0.212)	143/137	1.03	(0.72-1.49)	158/228	1.18	(0.88-1.58)
	176/202	0.88	(0.62-1.24)	127/161	1.25	(0.91-1.71)
	210/248	0.90	(0.64-1.26)	82/126	1.04	(0.73-1.47)
		P=0.410			P=0.561	
cis MUFA	139/149	1.00	-	142/236	1.00	-
(P=0.431)	151/150	1.06	(0.76-1.48)	151/214	1.11	(0.81-1.51)
	175/187	0.98	(0.71-1.35)	115/189	0.87	(0.63-1.21)
	171/210	0.88	(0.64-1.21)	119/166	1.06	(0.76-1.49)
		P=0.337			P=0.988	
Omega-6 PUFA	196/177	1.00	-	126/167	1.00	-
(P=0.068)	169/166	0.89	(0.66-1.21)	117/214	0.73	(0.52-1.03)
	141/182	0.69	(0.51-0.94)	131/212	0.81	(0.58-1.13)
	130/171	0.69	(0.50-0.95)	153/212	0.95	(0.68-1.32)
		P=0.011			P=0.844	
Omega-3 PUFA	168/160	1.00	-	128/210	1.00	-
(P=0.029)	175/172	0.94	(0.67-1.29)	120/199	0.94	(0.68-1.31)
	160/183	0.82	(0.60-1.12)	127/196	0.97	(0.70-1.34)
	133/181	0.72	(0.53-1.00)	152/200	1.16	(0.84-1.60)
		P=0.033			P=0.282	
Trans fatty acids	131/141	1.00	-	140/254	1.00	-
(P=0.903)	141/179	0.85	(0.61-1.19)	136/210	1.14	(0.83-1.56)

	Below Median			Above median		
Dietary fatty acids	**No of cases/controls**	**OR**	**95% CI**	**No of cases/controls**	**OR**	**95% CI**
	155/189	0.86	(0.62-1.20)	134/188	1.17	(0.85-1.61)
	209/187	1.14	(0.83-1.57)	117/153	1.16	(0.83-1.64)
		P=0.282			P=0.354	

MUFA:Mono unsaturated fatty acids, PUFA: poly unsaturated fatty acids., Median=18.6g

OR: adjusted for age, gender, biospecimen type (blood vs. others), total calcium intake, physical activities in their 30s, body mass index, family history of colorectal cancer, pack-years of cigarette smoking and postmenopausal hormone use (women), highest education achieved, and NSAID use.

P-values following the last ORs for each fatty acid are for a linear trend with the median intake of quartiles of each fatty acid and p-values in the parentheses are for interaction with fiber