RESEARCH COMMUNICATION

# Serum Concentrations of Fatty Acids and Colorectal Adenoma Risk: A Case-Control Study in Japan

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## Abstract

**Background: Epidemiologic studies of n-3 fatty acids (FAs) and risk of colorectal cancer have generated inconsistent results, and relations with precursor colorectal adenomas (CRA) have not been evaluated in detail. We here focused on possible associations of serum FAs with CRA in the Japanese population. Methods: We conducted a case-control study of 203 asymptomatic CRA cases (148 men, 55 women) and 179 healthy controls (67 men, 112 women) during 1997-2003 in Nagoya, Japan. Baseline information was obtained using a lifestyle questionnaire and serum FA levels were measured by gas chromatography. Results: A non-significant inverse association with CRA was observed for eicosapentaenoic acid (EPA) among women. Moreover, the concentrations of docosahexaenoeic acid (DHA), a major component of n-3 highly-unsaturated FAs (HUFAs), were significantly lower in cases in both sexes. In addition, serum concentrations of total FAs, saturated FAs (SFAs) and mono-unsaturated FAs (MUFAs) had strong positive links with CRA risk. In contrast, arachidonic acid (AA) and DHA were inversely related, with 66% and 59% risk reduction, respectively. Ratios of SFAs/n-3 PUFAs and SFAs/n-3 HUFAs exhibited significant positive relations with CRA risk but there was no clear link with n-6 PUFAs/n-3 PUFAs. Conclusions: Our findings suggest a promoting influence of SFAs and MUFAs along with a protective effect of DHA on CRA risk. However, further research is needed to investigate the observed discrepancy with the generally accepted roles of the AA cascade in carcinogenesis.**

**Key Words:** Colorectal adenomas - fatty acids – biomarkers - serum concentrations

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## Introduction

Colorectal adenomas (CRA), assumed to be precursors of colorectal cancer (CRC) (Durno, 2007), are usually asymptomatic and are most commonly detected by chance in individuals undergoing colonoscopy or sigmoidoscopy for screening. They occur about a decade before clinical diagnosis of CRC. It has been hypothesized that dietary and lifestyle factors that influence CRC development may also affect the CRA risk (Jacobs et al., 2007; Miller et al., 2007). Of possible dietary factors, intake of fat and fatty acids (FAs) has long been a matter of interest.

Earlier studies focused on the relationships between risk and total fat and saturated FAs (Slattery et al., 1997; Nkondjock et al., 2003), but recently n-3 poly-unsaturated FAs (PUFAs) and n-3 highly-unsaturated FAs (HUFAs), including eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) derived from sea foods (Petrik et al., 2000; Fritsche, 2006; Stehr and Heller, 2006), have received increasing attention due to their potential roles in inflammatory processes, tumorigenesis, angiogenesis and cell proliferation (James et al., 2000; Larsson et al., 2004; Kimura, 2006). Results of animal and ecologic studies have suggested that n-3 PUFAs might reduce the risk of CRA/CRC (Caygill and Hill, 1995; Pietinen et al., 1999; Roynette et al., 2004). Moreover, clinical trials have found that n-3 PUFAs supplementation reduced cell proliferation (Anti et al., 1994; Tokudome et al., 2002; Cheng et al., 2003).

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However, the relationship between these FAs and CRC has been inconsistent in epidemiologic research. Some prospective (Pietinen et al., 1999; Terry et al., 2001) and case-control (Slattery et al., 1997; Busstra et al., 2003) studies reported no significant associations between n-3 PUFAs and risk of CRA/CRC, whereas one case-control study showed statistically significant inverse trends (Nkondjock et al., 2003).

Conversely, n-6 PUFAs are suggested to have a critical role in CRC promotion through cyclooxygenase (COX) and lipoxygenase pathways involved in the arachidonic acid (AA) cascade (Rao and Reddy, 1993; Poole et al., 2007). However, some epidemiologic studies indicated these FAs have no influences on colorectal carcinogenesis (Terry et al., 2001; Busstra et al., 2003; Theodoratou et al., 2007), while other reports noted the protective effects of n-6 PUFAs, especially AA, on CRA/CRC (Kojima et al., 2005; Kuriki et al., 2006).

As previous investigations of intake and serum concentrations of n-3 and n-6 PUFAs in relation to CRA/CRC risk have been inconclusive, we here focused on associations of serum FAs, especially n-3 PUFAs and n-3 HUFAs, with CRA, precursor lesions of CRC, to find potential risk factors in the Japanese population, which has the highest consumption of sea foods as a main source of n-3 PUFAs, especially n-3 HUFAs.

## Materials and Methods

*Study Subjects*

This case-control study was conducted as part of a research program on dietary and lifestyle factors related to the colorectal adenoma-carcinoma sequence in Nagoya, Japan.

Cases consisted of consecutive patients, aged from 35-75 years, with histologically-verified colorectal adenomatous polyp/polyps, who were admitted to Nagoya City University Hospital and agreed to participate in this study during 1997-2003. These subjects are part of a randomized control trial which has been continuously conducted since 1997 (Tokudome et al., 2002). The lesions included grade 3 adenomas with light/moderate atypia, grade 4 adenomas with severe atypia and grade 5 small adenocarcinomas (carcinoma *in situ*) according to the General Rules for Clinical and Pathological Studies on Cancers of the Colon, Rectum and Anus (Japanese Society for Cancer of Colon and Rectum, 1998).

Controls were selected from volunteer participants who had a negative faecal occult blood test for screening examinations for CRA and CRC, during the period of case collection at Naka Health Center, Nagoya. Subjects were 205 CRA cases and 181 controls with no history of familial adenomatous polyposis or hereditary non-polyposis colorectal cancer, bleeding diathesis or a past history of CRC, gastrectomy or cholecystectomy. Two patients, who had CRAs with a small *in situ* carcinoma, were included in the cases . Finally, after exclusion of 3 subjects (1 case, 2 controls) with extremely high serum FAs (more than mean ± 3SD), 203 CRA cases (148 men, 55 women) and 179 healthy controls (67 men, 112 women) were analyzed.

The Internal Review Board of the Nagoya City University Graduate School of Medical Sciences approved the research protocol, and all subjects provided written informed consent.

*Lifestyle questionnaire*

Detailed information on demographic characteristics, personal medical history, usual leisure-time physical activity/exercise, cigarette smoking and alcohol drinking, intake of supplements and history of CRA or CRC in first-degree relatives was collected by trained interviewers. Smokers were defined as those who had ever smoked cigarettes daily for at least 1 year, and smoking status was classified into 3 categories (never, past or current smoker). The consumption of five types of alcoholic beverages (beer, whisky, wine, sake and shochu) over the past years was categorized into never, past or current drinker. Also, history of hyperlipidemia includes cases under treatment or observation of hypercholesterolemia and/or hypertriglyceridemia.

*Measurements of serum FAs*

All participants were asked to provide 7 ml of overnight fasting venous blood, the sampling tubes being immediately placed in a 4°C refrigerator. Within 4 hours of blood collection, blood was separated into plasma, buffy coat (layer of white blood cells) and red blood cells (by centrifugation at 2,500 rpm for 15 min at 4°C, aliquoted into four tubes, and immediately stored at -80°C until analysis of FAs by gas chromatography as previously reported (Kuriki et al., 2002). The analyzers of FAs were completely blinded to information on study subjects. The precision of FA measurements in plasma intra- and inter assay coefficients of variation ranged from 1.8 to 4.8 and 2.5 to 7.2 %, respectively (Kuriki et al., 2003). Each plasma FA level was expressed as the absolute concentration (mg/dL).

*Selected FAs and grouping*

We measured the following 13 FAs: 14:0 (myristic acid); 16:0 (palmitic acid); 16:1n-7 (palmitoleic acid); 18:0 (stearic acid); 18:1n-9 (oleic acid); 18:2n-6 (linoleic acid, LA); 18:3n-6 (α-linolenic acid, GLA); 18:3n-3 (α-linolenic acid, ALA); 20:3n-6 (dihomo-α-linolenic acid, DGLA); 20:4n-6 (AA); 20:5n-3 (EPA); 22:5n-3 (DPA); 22:6n-3 (DHA).

We calculated mean compositions and concentrations of serum FAs and summarized the data into the following seven groups: SFAs (14:0 + 16:0 + 18:0); MUFAs (16:1n-7 + 18:1n-9); PUFAs (n-6 PUFAs + n-3 PUFAs); n-6 PUFAs (LA + GLA + DGLA + AA); n-3 PUFAs (ALA + n-3 HUFAs); and n-3 HUFAs (EPA + DPA + DHA). We also defined the ratios of specific FAs as follows: SFAs/n-6 PUFAs; SFAs/n-3 PUFAs; SFAs/n-3 HUFAs; n-6 PUFAs/n-3 PUFAs; n-6 PUFAs/n-3 HUFAs; AA/EPA; and AA/DHA.

*Statistical analysis*

We first compared the background characteristics between cases and controls using Student's *t*- test or analysis of variance for means, and the $x^2$ test or Cochran-Mantel-Haenszel $x^2$ test for proportions by sex.

**Table 1. Basic Characteristics of Colorectal Adenoma Cases and Controls by Sex**

| | Men | | Women | |
|---|---|---|---|---|
| | Cases (n= 148) | Controls (n= 67) | Cases (n=55) | Controls (n=112) |
| Age in years (Mean ± SD) | 59.5 ± 9.2 | 60.1 ± 10.8 | 60.1 ± 8.7 | 60.7 ± 9.1 |
| *p* value[1] | 0.503 | | 0.674 | |
| Body mass index (Mean ± SD) | 23.6 ± 3.0 | 23.3 ± 2.6 | 23.0 ± 3.6 | 22.6 ± 2.8 |
| *p* value | 0.641 | | 0.48 | |
| Family history of colorectal adenoma or cancer (%)[2] | 16 (10.7%) | 3 (4.8%) | 8 (14.5%) | 6 (5.6%) |
| *p* value | 0.05 | | 0.05 | |
| Smoking history (%) | | | | |
| Current smoker | 64 (43.3%) | 13 (19.4%) | 10 (18.2%) | 7 (6.3%) |
| Former smoker | 68 (45.9%) | 27 (40.3%) | 4 (7.3%) | 2 (1.8%) |
| Never smoker | 16 (10.8%) | 27 (40.3%) | 41 (74.5%) | 103 (91.9%) |
| *p* value | 0.001 | | 0.008 | |
| Alcohol drinking history (%) | | | | |
| Current drinker | 115 (77.7%) | 40 (59.8%) | 13 (23.7%) | 25 (22.3%) |
| Former drinker | 7 (4.7%) | 6 (8.9%) | 1 (1.8%) | 5 (4.5%) |
| Never drinker | 26 (17.6%) | 21 (31.3%) | 41 (74.5%) | 82 (73.2%) |
| *p* value | 0.015 | | 0.682 | |
| Leisure-time physical activity/ exercise (yes) (%) | 101 (68.2%) | 38 (56.7%) | 33 (54.5%) | 52 (46.4%) |
| *p* value | 0.09 | | 0.075 | |
| History of hyperlipidemia (%) [3] | 23 (15.6%) | 18 (26.9%) | 16 (29.1%) | 23 (20.5%) |
| *p* value | 0.052 | | 0.246 | |
| History of diabetes (%) | 6 (4.1%) | 3 (4.4%) | 1 (1.8%) | 5 (4.5%) |
| *p* value | 0.401 | | 0.322 | |

[1] Each *p* value is based on the Chi-square test for categorical and on the *t*-test for continuous variables . [2]Family history of colorectal adenomas or cancers in the first-degree relatives was considered. [3]History of hyperlipidemia includes cases under treatment or observation of hypercholesterolemia and/or hypertrigly ceridemia

Unconditional logistic regression models were used to calculate odds ratios (ORs) for the incidence of CRA for each FA. Blood levels of FAs were divided into quartiles based on the FA distributions in the controls. ORs were calculated for the second quartile (Q2), third quartile (Q3), and highest quartile (Q4) versus the lowest quartile (Q1). To test for linear trends in ORs over quartiles, we coded each quartile as 0, 1, 2 or 3 and incorporated these data into the logistic model as a single variable.

We adjusted for the following factors by including them in the logistic model: age; body mass index (weight (kg)/height (m)$^2$; <20, 20.0-24.9, or ≥25.0) calculated from reported height and weight; history of CRA or CRC in the first-degree relatives (yes or no); history of diabetes (yes or no); smoking status (never, past, or current); daily alcohol consumption (never, former, or current); vigorous exercise (yes or no) and season of data collection. In Japan, regular users of non-steroidal anti-inflammatory drugs are very few (Kuriki et al., 2006), and we did not include this factor in our model.

All statistical analyses were conducted using SPSS version 15, and $p$ <0.05 was considered statistically significant.

## Results

Table 1 shows the basic characteristics of subjects participating in the study by sex. There were no significant differences between cases and controls regarding age and body mass index in either sex, but smoking and drinking habits were more frequent in cases than controls. The cases were also more likely to have a family history of CRA or CRC in first-degree relatives. However, the two groups did not differ in variables for physical exercise and history of diabetes. A significantly lower proportion of history of hyperlipidemia was observed in cases than controls for males, but a non-significant inverse pattern was found for females.

Serum FA concentrations in case and control subjects are shown in Table 2. The multivariate adjusted mean values for serum SFAs, including myristic acid, palmitic acid and stearic acid in cases were significantly higher than in controls in both sexes. Similarly, serum MUFAs were higher among cases. For n-6 PUFAs, LA and GLA values in cases and controls were almost the same. Also, DGLA was significantly higher in cases, whereas the mean value for AA was lower. Among n-3 PUFAs, ALA compositions did not differ significantly between cases and controls for either sex. For EPA, the lower serum values in cases were not significantly different from those of controls for either sex. However, the concentrations of DHA, a major component of n-3 HUFAs, were lower in cases than controls, while values for DPA, a minor component, were higher. Ratios of SFAs/n-6 PUFAs, SFAs/n-3 PUFAs and SFAs/n-3 HUFAs in both males and females exhibited positive significant associations with CRA risk, but there were no obvious associations for n-6 PUFAs/n-3 PUFAs, n-6 PUFAs/n-3 HUFAs and AA/DHA.

When we conducted a stratified analysis in non-smoker women, all of the above-mentioned relations between CRA and FAs, including total FAs, SFAs, MUFAs, AA, EPA, DPA and DHA, remained alike (data not shown).Moreover, the compositions of total n-3 PUFAs, n-3 HUFAs, EPA, DHA and AA were significantly lower

**Table 2. Serum Fatty Acid Concentrations in Colorectal Adenoma Cases and Controls by Sex**

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Serum Fatty acids (mg/dL) [1,2] | Cases (n= 148) | Controls (n= 67) | p-value | Cases (n=55) | Controls (n=112) | p-value |
| Total Fatty acids (FAs) | 350.42 (6.37) | 322.72 (6.22) | 0.01 | 315.98 (6.98) | 303.16 (3.89) | 0.05 |
| SFAs (Saturated FAs) | 116.13 (5.89) | 100.33 (6.49) | 0.001 | 100.05 (4.28) | 92.06 (4.57) | 0.01 |
| 14:0 (Myristic acid) | 3.12 (0.31) | 2.43 (0.34) | 0.005 | 2.68 (0.28) | 2.01 (0.30) | 0.002 |
| 16:0 (Palmitic acid) | 82.21 (4.24) | 73.05 (4.67) | 0.007 | 72.09 (3.21) | 67.08 (3.43) | 0.03 |
| 18:0 (Stearic acid) | 30.80 (2.87) | 24.87 (3.16) | 0.01 | 25.30 (1.05) | 22.98 (1.12) | 0.003 |
| MUFAs (Mono-unsaturated FAs) | 90.87 (5.43) | 78.39 (5.98) | 0.004 | 78.59 (3.91) | 73.34 (4.18) | 0.05 |
| 16:1n-7 (Palmitoleic acid) | 11.85 (0.92) | 8.82 (1.01) | 0.001 | 10.18 (0.71) | 7.81 (0.76) | 0.001 |
| 18:1n-9 (Oleic acid) | 79.01 (4.64) | 69.57 (5.11) | 0.01 | 68.41 (3.44) | 65.54 (3.67) | 0.252 |
| PUFAs (Poly-unsaturated FAs) | 144.11 (5.83) | 144.20 (6.43) | 0.693 | 137.36 (4.61) | 137.76 (4.93) | 0.988 |
| n-6 PUFAs (Poly-unsaturated FAs) | 113.07 (4.80) | 112.39 (5.29) | 0.859 | 109.29 (4.03) | 108.15 (4.31) | 0.697 |
| 18:2n-6 (Linoleic acid) | 87.69 (4.08) | 86.64 (4.49) | 0.747 | 86.64 (3.62) | 83.33 (3.86) | 0.21 |
| 18:3n-6 (α- linolenic acid) | 1.30 (0.14) | 1.17 (0.16) | 0.272 | 0.98 (0.11) | 0.92 (0.12) | 0.518 |
| 20:3n-6 (Dihomo-α- linolenic acid) | 4.59 (0.35) | 3.98 (0.38) | 0.03 | 4.32 (0.34) | 3.38 (0.37) | 0.001 |
| 20:4n-6 (Arachidonic acid) (AA) | 19.49 (1.04) | 20.60 (1.15) | 0.183 | 17.36 (0.88) | 20.52 (0.94) | 0.001 |
| n-3 PUFAs (Poly-unsaturated FAs) | 31.06 (2.19) | 31.81 (2.42) | 0.511 | 28.07 (2.07) | 29.61 (2.21) | 0.431 |
| 18:3n-3 (α-linolenic acid) | 3.06 (0.26) | 2.98 (0.29) | 0.696 | 2.84 (0.27) | 2.63 (0.29) | 0.278 |
| n-3 HUFAs (Highly-unsaturated FAs) | 28.08 (2.09) | 28.84 (2.30) | 0.527 | 25.23 (1.99) | 26.98 (2.12) | 0.183 |
| 20:5n-3 (Eicosapentaenoic acid) | 8.31 (0.95) | 8.37 (1.05) | 0.222 | 7.61 (0.91) | 8.24 (0.97) | 0.12 |
| 22:5n-3 (Docosapentaenoic acid) | 2.37 (0.29) | 1.95 (0.32) | 0.001 | 2.25 (0.25) | 1.65 (0.27) | 0.001 |
| 22:6n-3 (Docosahexaenoic acid) | 17.42 (1.16) | 18.52 (1.28) | 0.06 | 15.37 (1.14) | 17.09 (1.22) | 0.04 |
| SFA /n-6 PUFAs | 1.01 (0.02) | 0.89 (0.02) | 0.001 | 0.92 (0.02) | 0.85 (0.01) | 0.02 |
| SFA /n-3 PUFAs | 3.74 (0.13) | 3.18 (0.11) | 0.007 | 3.54 (0.20) | 3.11 (0.08) | 0.001 |
| SFA /n-3 HUFAs | 4.13 (0.15) | 3.78 (0.14) | 0.01 | 3.96 (1.89) | 3.41 (1.14) | 0.001 |
| n-6 PUFAs /n-3 PUFAs | 3.63 (0.28) | 3.54 (0.31) | 0.98 | 3.87 (0.39) | 3.65 (0.42) | 0.269 |
| n-6 PUFAs /n-3 HUFAs | 4.08 (0.35) | 3.89 (0.39) | 0.953 | 4.31 (0.48) | 4.01 (0.51) | 0.233 |
| AA/EPA | 2.39 (0.31) | 2.48 (0.34) | 0.33 | 2.31 (0.48) | 2.51 (0.52) | 0.278 |
| AA/DHA | 1.14 (0.09) | 1.12 (0.10) | 0.65 | 1.13 (0.12) | 1.21 (0.13) | 0.746 |

[1] Values are expressed as the mean (SE; standard error) absolute serum fatty acids (mg/dL) [2]Adjusted for age, body mass index, history of colorectal adenomas/cancers in first-degree relatives, history of diabetes, smoking, drinking, physical activity and season of data collection

in cases than controls, while values for SFAs and MUFAs were higher in the case group (data not shown).

As shown in Table 3, total FAs, SFAs and MUFAs were significantly associated with CRA risk. Compared with the lowest quartiles, multivariate adjusted ORs for the highest quartiles of total SFAs and MUFAs were 4.42 and 4.99 in males (95% CI, 1.52-12.87 and 1.56-15.95, *p* for trend < 0.01) and 4.69 and 2.55 in females (95% CI, 1.45-15.14 and 0.84-7.71, *p* for trend < 0.01), respectively. Also, ORs for associations between SFAs and MUFAs with CRA risk were higher in large adenomas (≥ 1 cm) than small type (data not shown).

Although there were no associations between total n-6 PUFAs, LA and GLA with CRA risk, AA was linked with a significant decrease in females, and with a similar non-significant trend among males. In contrast, increased risk was found with DGLA in both sexes (ORs, 2.65 and 3.05 for men and women, respectively) (data not shown). With n-3 HUFAs, an inverse dose-response relationship was evident for DHA among females, but not among men. This inverse association was more prominent in colon adenomas (data not shown). Also, non-significant associations between EPA and CRA risk were further noted, but with opposing directions in men and women.

## Discussion

In this study, serum concentrations of EPA were rather lower in cases than controls among women. However, the concentrations of DHA were significantly lower in cases in both sexes, suggesting a protective effect of DHA, a major component of n-3 HUFAs, on CRA. In addition, serum concentrations of total FAs, SFAs and MUFAs demonstrated strong positive associations with CRA risks. In contrast, AA and DHA were inversely related to CRA, with 66% and 59% risk reductions, respectively.

In our study, the values for total n-3 PUFAs and n-3 HUFAs were slightly lower in cases among women, even though dose-response relations with CRA risk were not statistically significant.

We also found a non-significant association of EPA with CRA among women, whereas men exhibited an opposite pattern, although the mean values of serum compositions of EPA were significantly lower in cases than controls. However, these observations are concordant with the findings of three case-control studies which were based on biomarkers of FAs in association with CRC, showing that the protective effects of EPA were not evident (Kojima et al., 2005; Kuriki et al., 2006; Hall et al., 2007). In this study, the relation between DPA and CRA risk was incompatible with other studies indicating no associations between this FA and CRC risk (Nkondjock et al., 2003; Kuriki et al., 2006; Hall et al., 2007). However, only one nested case-control study found an inverse association with CRC risk in men (Kojima et al., 2005). Thus, further studies are needed to evaluate the role of DPA, as a minor component of n-3 HUFAs, in carcinogenesis. In contrast, results of DHA are compatible with findings of the above-

**Table 3. Association Between Serum Fatty Acid Concentrations and Colorectal Adenoma Risk by Sex**

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Serum fatty acids (mg/dL) | Value [1] | Cases/Controls | OR (95% CI) [2,3] | Value | Cases/Controls | OR (95% CI) |
| Total fatty acids (FAs) | <262.70 | 18/17 | 1:00 | <272.37 | 12/28 | 1:00 |
| | 262.70-306.40 | 35/17 | 2.36 (0.79-7.08) | 272.37-292.95 | 7/28 | 0.54 (0.14-2.02) |
| | 306.41-342.80 | 41/17 | 2.70 (0.93-7.87) | 292.96-324.37 | 16/28 | 1.54 (0.51-4.63) |
| | >342.80 | 52/16 | 3.58 (1.20-10.7) | >324.37 | 20/28 | 2.05 (0.73-5.78) |
| *p* for trend | | | 0.027 | | | 0.052 |
| SFAs (saturated FAs) | <78.40 | 19/17 | 1:00 | <78.90 | 6/29 | 1:00 |
| | 78.40-92.8 | 28/17 | 2.13 (0.69-6.51) | 78.90-88.50 | 10/27 | 1.93 (0.54-6.89) |
| | 92.81-105.40 | 38/17 | 2.78 (0.92-8.38) | 88.51-97.20 | 14/28 | 2.21 (0.60-8.12) |
| | >105.40 | 61/16 | 4.42 (1.52-12.87) | >97.20 | 25/28 | 4.69 (1.45-15.14) |
| *p* for trend | | | 0.007 | | | 0.009 |
| MUFAs* - | <59.50 | 14/17 | 1:00 | <59.95 | 9/28 | 1:00 |
| | 59.50-67.90 | 17/18 | 1.69 (0.49-5.83) | 59.95-66.05 | 5/28 | 0.49 (0.12-2.10) |
| | 67.91-86.10 | 55/16 | 4.48 (1.51-13.31) | 66.06-77.13 | 17/28 | 2.13 (0.69-6.58) |
| | >86.10 | 60/16 | 4.99 (1.56-15.95) | >77.13 | 24/28 | 2.55 (0.84-7.71) |
| *p* for trend | | | 0.002 | | | 0.015 |
| n-6 PUFAs* | <95.90 | 44/17 | 1:00 | <99.50 | 15/29 | 1:00 |
| | 95.90-108.30 | 30/17 | 0.95 (0.34-2.67) | 99.50-107.15 | 10/27 | 0.40 (0.12-1.40) |
| | 108.31-126.70 | 40/17 | 1.63 (0.57-4.63) | 107.16-121.15 | 15/28 | 0.79 (0.27-2.27) |
| | >126.70 | 32/16 | 0.67 (0.24-1.84) | >121.15 | 15/28 | 0.86 (0.29-2.58) |
| *p* for trend | | | 0.727 | | | 0.906 |
| 18:2n-6 (Linoleic acid) | <74.40 | 46/17 | 1:00 | <75.70 | 12/28 | 1:00 |
| | 74.40-83.00 | 17/17 | 0.69 (0.23-2.06) | 75.70-82.65 | 12/28 | 0.66 (0.21-2.13) |
| | 83.01-98.80 | 47/17 | 1.74 (0.64-4.71) | 82.66-93.87 | 8/28 | 0.56 (0.16-1.90) |
| | >98.80 | 36/16 | 0.86 (0.31-2.36) | >93.87 | 23/28 | 1.54 (0.54-4.36) |
| *p* for trend | | | 0.813 | | | 0.235 |
| 20:4n-6 (Arachidonic acid) | <17.40 | 67/19 | 1:00 | <18.05 | 30/28 | 1:00 |
| | 17.40-19.90 | 24/15 | 0.60 (0.21-1.68) | 18.05-20.50 | 16/29 | 0.49 (0.19-1.24) |
| | 19.91-22.50 | 28/18 | 0.58 (0.21-1.60) | 20.51-22.38 | 5/27 | 0.11 (0.28-0.45) |
| | >22.50 | 27/15 | 0.52 (0.19-1.42) | >22.38 | 4/28 | 0.11 (0.03-0.43) |
| *p* for trend | | | 0.104 | | | 0.001 |
| n-3 PUFAs* | <23.90 | 44/17 | 1:00 | <24.53 | 19/28 | 1:00 |
| | 23.90-29.10 | 41/17 | 0.97 (0.36-2.63) | 24.53-27.75 | 10/28 | 0.47 (0.15-1.40) |
| | 29.11-32.80 | 21/18 | 0.47 (0.16-1.41) | 27.76-35.78 | 16/28 | 0.58 (0.21-1.67) |
| | >32.80 | 40/15 | 0.81 (0.35-2.73) | >35.78 | 10/28 | 0.71 (0.23-2.14) |
| *p* for trend | | | 0.858 | | | 0.487 |
| 18:3n-3 (α linolenic acid) | <2.10 | 50/20 | 1:00 | <1.93 | 14/28 | 1:00 |
| | 2.10-2.60 | 29/17 | 0.82 (0.29-2.34) | 1.93-2.45 | 13/28 | 1.05 (0.35-3.17) |
| | 2.61-3.20 | 20/14 | 0.59 (0.20-1.76) | 2.46-2.90 | 8/31 | 0.43 (0.13-1.41) |
| | >3.20 | 47/16 | 1.12 (0.43-2.90) | >2.90 | 20/25 | 1.75 (0.64-4.83) |
| *p* for trend | | | 0.675 | | | 0.201 |
| n-3 HUFAs * | <21.80 | 50/18 | 1:00 | <21.32 | 18/28 | 1:00 |
| | 21.80-26.50 | 35/16 | 0.89 (0.32-2.43) | 21.32-25.20 | 13/29 | 0.58 (0.21-1.65) |
| | 26.51-29.50 | 21/17 | 0.54 (0.19-1.56) | 25.21-32.77 | 15/27 | 0.61 (0.21-1.78) |
| | >29.50 | 40/16 | 0.86 (0.28-2.21) | >32.77 | 9/28 | 0.54 (0.19-1.54) |
| *p* for trend | | | 0.94 | | | 0.429 |
| 20:5n-3 EPA* | <5.70 | 42/19 | 1:00 | <5.50 | 18/29 | 1:00 |
| | 5.70-7.80 | 36/15 | 1.14 (0.42-3.13) | 5.50-8.20 | 17/30 | 0.65 (0.23-1.86) |
| | 7.81-9.50 | 24/17 | 0.95 (0.31-2.87) | 8.21-10.48 | 7/25 | 0.29 (0.08-0.99) |
| | >9.50 | 44/16 | 1.22 (0.48-3.54) | >10.48 | 13/28 | 0.62 (0.22-1.80) |
| *p* for trend | | | 0.167 | | | 0.373 |
| 22:5n-3 DHA* | <1.10 | 7/18 | 1:00 | <1.00 | 3/32 | 1:00 |
| | 1.10-1.40 | 12/18 | 2.56 (0.63-10.41) | 1.00-1.30 | 4/29 | 1.79 (0.27-11.90) |
| | 1.41-1.70 | 25/16 | 7.96 (1.89-33.45) | 1.31-1.80 | 11/25 | 9.52 (1.62-55.56) |
| | >1.70 | 102/15 | 23.12 (6.73-73.21) | >1.80 | 37/26 | 16.32 (3.35-69.85) |
| *p* for trend | | | 0.001 | | | 0.001 |
| 22:6n-3DHA* | <14.20 | 67/17 | 1:00 | <13.83 | 21/28 | 1:00 |
| | 14.20-16.10 | 25/17 | 0.39 (0.14-1.09) | 13.83-16.35 | 15/28 | 0.83 (0.30- 2.24) |
| | 16.11-19.20 | 24/17 | 0.33 (0.12-0.95) | 16.36-20.15 | 12/28 | 0.52 (0.18-1.50) |
| | >19.20 | 30/16 | 0.40 (0.15-1.09) | >20.15 | 7/28 | 0.43 (0.14-1.38) |
| *p* for trend | | | 0.055 | | | 0.036 |
| n-6 PUFAs/ n-3 PUFAs | <3.30 | 42/21 | 1:00 | <3.00 | 10/30 | 1:00 |
| | 3.30-4.00 | 36/15 | 1.01 (0.37-2.72) | 3.00-3.70 | 10/27 | 0.63 (0.19-2.11) |
| | 4.01-4.80 | 31/17 | 1.58 (0.57-4.42) | 3.71-4.75 | 17/27 | 1.30 (0.43-3.91) |
| | >4.80 | 37/14 | 1.06 (0.37-3.06) | >4.75 | 18/28 | 1.63 (0.54-4.99) |
| *p* for trend | | | 0.656 | | | 0.249 |

[1]Values are expressed as absolute serum fatty acids (mg/dL) as quartile categories. [2]OR, Odds ratio; CI, confidence interval. [3] Adjusted for age, BMI, history of colorectal adenoma/cancer in first-degree relatives, history of diabetes, smoking, drinking, physical activity and season of data collection. #MUFAs (Mono-unsaturated FAs), PUFAs(Poly-unsaturated FAs), HUFAs(Highly-unsaturated FAs), (EPA)(Eicosapentaenoic acid), (DPA)(Docosapentaenoic acid), DHA (Docosahexaenoic acid)

mentioned studies (Kojima et al., 2005; Kuriki et al., 2006), which supported the preventive role of DHA in CRC carcinogenesis. The tumor growth suppressing mechanisms of n-3 HUFAs are thought to be due to generation of eicosanoid mediators with biological activity (Jones et al., 2003), modulation of signal transduction and gene expression with subsequent induction of apoptosis (Kubota et al., 1998; Cheng et al., 2003; Gutt et al., 2007), modulation of insulin sensitivity (Larsson et al., 2004; Kuriki et al., 2007), proteasomal regulation of beta-catenin levels and alteration expression of T-cell factor beta-catenin target genes (Calviello et al., 2007), production of free radicals and reactive oxygen species (Bartsch et al., 1999; Stoll, 2002) and changes in estrogen metabolism (Larsson et al., 2004).

Also, the serum AA value was associated with reduced CRA risk in women, although not men, in line with the reverse associations reported in two case-control studies in Japan in which the erythrocyte and serum compositions of FAs were measured (Kojima et al., 2005; Kuriki et al., 2006). Another study in the US also indicated blood levels of AA to be lower in cancer cases than controls (Hall et al., 2007). Assays of AA in previous reports from the United Kingdom, Spain, and Russia similarly pointed to preventive roles of AA in those cases in breast cancer (Neoptolemos et al., 1988; Zaridze et al., 1990; Baro et al., 1998). The observations contrasted, however, with the findings from some animal and other epidemiologic studies, showing elevated levels of AA to be associated with increased risk of carcinogenesis (Neoptolemos et al., 1991; Pala et al., 2001; Nkondjock et al., 2003) by altering membrane phospholipid turnover, releasing membrane AA from phospholipid, and affecting prostaglandin synthesis via COX enzymes (Rao and Reddy, 1993). Although excessive intake of AA is considered to be involved in cell inflammation, proliferation and may impact carcinogenesis (Neoptolemos et al., 1991; Nkondjock et al., 2003), intake by Japanese of AA from meat, animal fat, chicken eggs, as main sources of AA, seems to be lower than in Western populations, and thus would not induce harmful effects (Moore et al., 2005).

ALA, a plant-derived n-3 PUFA and a precursor of EPA and DHA, did not demonstrate any link with CRA in the present study. This finding is compatible with previous epidemiologic studies in Japan and other countries (Slattery et al., 1997; Pietinen et al., 1999; Terry et al., 2001; Kuriki et al., 2006). Also, another Japanese study (Kojima et al., 2005), which measured serum FA levels, reported significant inverse and non-significant positive associations for ALA in relation to CRC risk in men and women, respectively. Mechanistic studies suggest that ALA might protect against carcinogenesis by decreasing prostaglandin production, suppressing COX-2 induction and proliferation in the colorectal mucosa (Brouwer et al., 2004).

Our observed significant positive associations between CRA risk and concentrations of SFAs, including myristic acid, palmitic acid and stearic acid, are consistent with previous investigations (Slattery et al., 1997; Kuriki et al., 2006), in line with SFA roles in cell signaling, insulin resistance pathway and regulation of membrane lipid fluidity and "gate-keeping" ability in colonic cells (Bruce et al., 2000; Zhou et al., 2000). Similarly, palmitoleic acid and total MUFAs were dose-dependently associated with increased risks in both sexes. Although a few studies have examined the relationship between MUFAs and CRA, they have not been conclusive. This is because MUFAs, especially oleic acid, have different mechanisms of action on carcinogenesis including an effect on hormonal status, modification of cell membrane structure and function, cell signaling transduction pathway and gene expression, and even modulate the function of the immune system (Escrich et al., 2007). However, our findings may support the hypothesis that MUFAs promote tumor growth (Schloss et al., 1997; Kojima et al., 2005) by increasing essential FA incorporation into cell membranes and also by interacting with the AA-cascade (Schmeits et al., 1999).

The inverse associations of EPA, DHA and AA with CRA risk were clearly more prominent in women than in men, suggesting a gender-CRA interaction, as supported by previous epidemiologic and experimental studies (Panis et al., 1990; Nkondjock et al., 2003). Genetic and hormonal factors, lifestyle and dietary habits, and disease are all thought to influence the FA metabolism. In addition, it has been suggested that female sex hormones are related to the sex-specific differences because they affect bowel transit time (Triadafilopoulos et al., 1998), bacterial fermentation in the colon, and particularly bile acid production (Potter, 1995; Grodstein et al., 1999).

Potential limitations that might affect interpretation of our results should be noted. First, although we used FA concentrations as biomarkers, several alternative methods are available for biologic assessment of fat intake. Levels in adipose tissues and erythrocyte membranes reflect long- and medium-term FA intake, respectively, whereas serum values reflect rather short-term (a week to several weeks) intake (Arab and Akbar, 2002). Second, we were unable to entirely exclude the possibility that there are subjects with false-negative faecal occult blood test. Third, the sample size was relatively small; therefore, we could not assess the CRA risk separately in terms of size, site, and grade, which are naturally important in evaluating the risk in relation to the adenoma-carcinoma sequence (Kimura et al., 2007). Fourth, the control group in this study was selected from health-conscious participants voluntarily undergoing screening examinations for CRC. Since they clearly paid especial attention to their health, they might not be completely representative of a Japanese general population.

In conclusion, we would like to stress that total FAs, especially SFAs and MUFAs, as important risk factors for CRA, should be restricted and replaced with n-3 HUFAs for the prevention of CRA/CRC. However, the protective effects of AA seem somewhat incompatible with the literature, and future studies should focus on generating a better understanding of the role played by AA cascade in the adenoma-carcinoma sequence in the colorectum.

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