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# FAT, FIBER, FRUITS, VEGETABLES, AND RISK OF COLORECTAL ADENOMAS

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**A case-control study was conducted at the National Naval Medical Center (Maryland, USA) from 1994 to 1996 to investigate the possible association between dietary factors and colorectal adenomas. Cases (*n* = 239) were subjects diagnosed with adenomas (146 new and 93 recurrent) by sigmoidoscopy or colonoscopy. Those with no evidence of adenomas found by sigmoidoscopy were recruited as controls (*n* = 228). Dietary variables, assessed by a 100-item food frequency questionnaire, were analyzed by the logistic regression model, which was adjusted for age, gender and total energy intake. Variables of fat intake were further adjusted for red meat intake. An increased risk of 7% [odds ratio (OR): 1.07; 95% confidence interval (95% CI): 0.94–1.22] per 5% energy/day from total fat was observed. Every additional 5% unit of oleic acid intake/day significantly increased the adenoma risk by 115% (OR: 2.15; 95% CI: 1.05–4.39). Red meat fat increased the risk by 20% (OR: 1.20; 95% CI: 0.71–2.04), and white meat fat decreased the risk by 67% (OR: 0.33; 95% CI: 0.19–0.95) for every additional 5% unit of respective intake/day. Risk decreased by 41% (OR: 0.59; 95% CI: 0.41–0.86) for every additional 5% unit of fiber intake/day. Vegetable [OR per 100 g of vegetable intake/day: 0.83, 95% CI: 0.67–1.04] and fruit (OR per 100 g of fruit intake/day: 0.92, 95% CI: 0.82–1.03) intake showed an inverse association, and the results are suggestive of an association with the risk for adenomas. In conclusion, a strong positive association between oleic acid intake and colorectal adenoma risk was observed. This is likely to be an indicator of "unhealthy" food (meat, dairy, margarine, mayonnaise, sweet baked food) consumption in this population. Increased intake of dietary fiber was associated with a moderately decreased risk of adenomas.**
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**Key words:** *colorectal adenoma; unsaturated fat; saturated fat; red meat fat; white meat fat; fiber; fruits and vegetables*

Colorectal cancer is the second leading cause of cancer deaths in the United States, accounting for approximately 10% of all cancer deaths.[1] Colorectal adenomas are considered to be potential precancerous lesions[2] and probably share a common etio-pathogenesis with colorectal cancer.[3] Epidemiologic studies have shown a positive association between fat and red meat[4–6] and an inverse association between dietary fiber, fruit and vegetable intake with the development of colorectal adenomas[7–10] However, the associations with more specific types of fats, fibers, fruits and vegetables are much less clear. Therefore, we investigated the associations between fat and its subtypes, fiber and its subtypes, fruits and vegetables and their subgroups in a sigmoidoscopy-based case-control study on colorectal adenomas.

## MATERIAL AND METHODS

The study was undertaken at the National Navy Medical Center (Bethesda, MD, USA) during 1994–1996. The details of the study have been published elsewhere.[6,11] Briefly, the cases ($n$ = 239) were subjects with new ($n$ = 146) or recurrent ($n$ = 93) adenomas diagnosed by sigmoidoscopy or colonoscopy and confirmed histologically. The controls ($n$ = 228) were subjects who were found to be free of adenomas on examination by sigmoidoscopy, during the same time period, and were frequency-matched to cases by age (± 5 years) and gender. The subjects were resident of the study area between the ages of 18 and 74 years and had never been diagnosed with Crohn's disease, ulcerative colitis or cancer (except nonmelanoma of the skin). The study was approved by the institutional review boards of both the National Cancer Institute and the National Naval Medical Center. Written informed consent was obtained from all participants. The participation rates were 84% for the cases and 74% for the controls.

A validated self-administered food frequency questionnaire, a modified version of the 100-item health habits and history questionnaire,[12] was used to obtain information on diet for the past 12 months before endoscopy. Frequencies of consumption as well as serving sizes were included in the questionnaire. Values for nutrient intake were computed by using the HHHQ-DIETSYS[13] software.

### *Data analysis*

Initially, mean intake (g/day) for the nutrient variables between new and recurrent adenoma cases were tested by $t$-statistic. In the absence of any significant differences, both new and recurrent adenomas were considered together for subsequent analysis. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using a logistic regression model[14] on continuous variables. ORs comparing the risk for disease at the 90$^{th}$ versus 10$^{th}$ percentiles were estimated, using logistic regression models also based on continuous variables as nutrient intake/(90$^{th}$ percentile of nutrient intake − 10$^{th}$ percentile of nutrient intake). The 10$^{th}$ and 90$^{th}$ percentiles of nutrient intake were based on the distribution of the control group. One of the advantages of this approach over the categorical comparison of exposure subgroups (*e.g.*, ≤ 10$^{th}$ percentile *vs.* ≥ 90$^{th}$ percentile) is that all subjects were included in the analysis, with concomitant increased power.

The linear relationship was checked by adding a quadratic term to the regression model, which was not statistically significant. Furthermore, kernel-smoothing regression was done to study the dose-exposure relationship nonparametrically. These plots then suggested that logistic-linear models were appropriate for continuous variables.[15]

All analyses were adjusted for age, gender and total energy intake. In a separate analysis, data for males and females were analyzed separately including sex as a potential confounder. The following factors were tested as potential confounders: family history of colorectal cancer (yes/no), pack year of cigarettes smoked (years), alcoholic beverage intake (g/day), ethnicity (non-Hispanic White/others), body mass index (continuous), physical activity (hours/week of vigorous and moderate activity), use of nonsteroidal antiinflammatory drugs (use of > 1 per week for at least 3 months prior to diagnosis/nonregular use) and red meat intake (g/day). Potential confounding was tested for each factor in separate models as well as for all factors in the same model. Variables that changed the risk estimate of interest by >10% were

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considered as potential confounders and were included in the model.

A multivariate nutrient-density method was used to adjust for energy by including nutrient intake in terms of percentage of total energy in calories as well as the total calorie intake in the regression model.[16] The risk estimates for fat and fiber (total and subtypes) variables were represented as an effect of a 5% unit change in energy from each type. Fat and fiber variables were specified in different subtypes and modeled simultaneously so that their total was equal to the total intake on each variable. We looked at addition effects, which represent the risk associated with adding the amount of each specific fat or fiber while keeping the consumption of fat or fiber from other sources constant.[17,18] The risk estimates for fruits and vegetables (all and subgroups) were represented as an effect of 100g/day increase in consumption. Fruits and vegetables are presented in g/day so as to be able to compare the odds ratios directly for related food items, and to see which ones are the most likely to be associated with increased or decreased risk.[18]

## RESULTS

Median age was higher in cases and with male preponderance. Family history of colorectal cancer was more common in cases. Cases smoked more, consumed alcoholic beverages more and were less likely to use nonsteroidal antiinflammatory drugs on a regular basis. The differences in body mass index or physical activity between cases and controls were small. Red meat consumption and total energy intake were higher among cases (Table I).

### *Fat*

Median ($10^{th}$, $90^{th}$ percentiles) intake of percentage of energy from various fats was as follows: 30 (19, 40) for total fat; 10 (6, 14) for saturated fatty acids; 20 (13, 27) for unsaturated fatty acids; 11 (7, 15) for oleic acid; 5 (3, 9) for linoleic acid; 7 (3, 12) for total meat fat; 5 (2, 10) for red meat fat; and 2 (0.5, 4) for white meat fat. The Spearman correlation coefficients ($r$) estimated from 228 sigmoidoscopy negative controls between total fat and its components such as saturated ($r = 0.90$), unsaturated ($r = 0.96$) and oleic acid ($r = 0.96$) *were high (Table II).*

Odds ratios for total fat and its components did not show a change of >10% except for red meat after adjusting for all potential confounders both separately and simultaneously. The effect of fat and its subtypes were attenuated by >10% after adjusting for red meat. Therefore red meat was included in these models apart from age, gender and total energy.

As a percent of total energy consumption, every additional 5% unit of total fat intake/day nonsignificantly increased the risk of adenomas by 7% (OR: 1.07; 95% CI: 0.94-1.22) (Fig. 1). The increased risk of 7% from total fat was partitioned into 17% (OR: 1.17; 95% CI: 0.89–1.54) increased risk for every additional 5% unit of unsaturated fatty acids intake/day and 11% (OR: 0.89; 95% CI: 0.55–1.44) decreased risk for every additional 5% unit of saturated fatty acids intake/day (Fig. 1). Further subdivision of unsaturated fatty acids into oleic acid, linoleic acid and other unsaturated fatty acids showed a statistically significant increased risk of 115% (OR: 2.15; 95% CI: 1.05–4.39) for every additional 5% unit of oleic acid intake/day, as well as decreased risks of 10% (OR: 0.90; 95% CI: 0.50–1.62) and 53% (OR:0.47; 95% CI:0.17–1.33) for every additional 5% unit of linoleic acid and other unsaturated fatty acid intake/day, respectively (Fig. 1). The ORs comparing $90^{th}$ to $10^{th}$ percentiles were 1.63 (95% CI: 0.68–3.95) for total fat, 1.90 (95% CI: 0.55–6.59) for unsaturated fatty acids, 11.62 (95% CI: 1.42–95.31) for oleic acid and 0.67 (95% CI: 0.27–1.67) for linoleic acid.

Subdivision of total fat intake into meat fat and fat from other sources resulted in a decreased risk of 13% (OR: 0.87; 0.57–1.34) per 5% unit of meat fat intake/day and an increased risk of 8% (OR: 1.08; 95% CI: 0.95–1.24) per 5% unit of other fat intake/day (Fig. 2). Further subdivision of meat fat showed 20% (OR: 1.20; 95% CI: 0.71–2.04) increased risk for every additional 5% unit of red meat fat intake/day and 57% (OR: 0.43; 95% CI: 0.19–0.95) decreased risk for every additional 5% unit of white meat fat intake/day. The ORs comparing $90^{th}$ to $10^{th}$ percentiles were 2.00 (95% CI: 0.57–7.02) for red meat fat, and 0.64 (95% CI: 0.39–1.06) for white meat fat.

### *Fiber*

Median ($10^{th}$, $90^{th}$ percentiles) intake of percentage of energy from various fibers was as follows: 6 (4, 11) for total fiber; 2 (1, 3) for vegetable fiber; 1.4 (0.4, 4) for fruit fiber; and 2 (1, 4) for grain fiber. Only age, gender and total energy intake were included in the model as none of the risk estimates for total fiber and its components were changed by >10% after adjusting for all potential confounders separately and simultaneously.

A statistically significant decreased risk for colorectal adenomas of 33% (OR: 0.67; 95% CI: 0.45–0.99) for every additional 5% unit of total fiber intake/day was observed (Fig. 3). On subdividing total fiber into vegetable, grain and fruit fiber, decreased risks of 10%, 31% and 39% were observed for every additional 5% unit of respective fiber intake/day (Fig. 3).

### *Fruits and vegetables*

Analysis of all fruits and vegetables and subgroups indicated that higher intake was associated with reduced risk for development of adenomas (Table III). However, none of the variables showed significant effect. Vegetable (OR per 100 g of vegetable intake/day: 0.83, 95% CI: 0.67–1.04) and fruit (OR per 100g of fruit intake/day: 0.92, 95% CI: 0.82–1.03) intake showed an inverse relationship, and the results are suggestive of an association with the risk for adenomas (Table III).

**TABLE I** – CHARACTERISTICS OF CASES WITH COLORECTAL ADENOMAS AND SIGMOIDOSCOPY-NEGATIVE CONTROLS, NATIONAL NAVY MEDICAL CENTER, MD, US, 1994–1996

| Characteristics | Cases ($n = 239$) | Controls ($n = 228$) |
|---|---|---|
| Female (%) | 23 | 37 |
| Ethnicity (%) | | |
| Non-Hispanic whites | 89 | 90 |
| Others | 11 | 10 |
| Colorectal cancer in family (%) | 16 | 12 |
| Nonsteroidal antiinflammatory drugs (%) | 52 | 65 |
| Age (yrs) | 60 (47, 72)[1] | 57 (46, 71)[1] |
| Body mass index (kg/m$^2$) | 27 (22, 32) | 26 (21, 32) |
| Physical activity (hr/wk) | 6 (0, 18) | 7 (1, 16) |
| Smoking (pack/year) | 5 (0, 58) | 0 (0, 33) |
| Alcoholic beverage (g/d) | 144 (0, 731.9) | 116.8 (0, 731.9) |
| Total calories (kcal/d) | 1567 (1026, 2506) | 1488 (943, 2349) |
| Red meat (g/d) | 50 (12, 113) | 36 (8, 91) |

[1]Median value (10th and 90th percentile).

**TABLE II** – SPEARMAN CORRELATION COEFFICIENTS OF FAT INTAKE AND ITS COMPONENTS ESTIMATED FROM 228 SIGMOIDOSCOPY-NEGATIVE CONTROLS, NATIONAL NAVY MEDICAL CENTER, MD, US, 1994–1996

| Fat and subtypes | Total fat | Saturated fatty acids | Unsaturated fatty acids | Oleic acid | Linoleic acid | Total meat fat | Red meat fat | White meat fat | Other source fat |
|---|---|---|---|---|---|---|---|---|---|
| Total fat | 1.00 | | | | | | | | |
| Saturated fatty acids | 0.90 | 1.00 | | | | | | | |
| Unsaturated fatty acids | 0.96 | 0.76 | 1.00 | | | | | | |
| Oleic acid | 0.96 | 0.84 | 0.94 | 1.00 | | | | | |
| Linoleic acid | 0.78 | 0.55 | 0.85 | 0.70 | 1.00 | | | | |
| Total meat fat | 0.38 | 0.40 | 0.33 | 0.42 | 0.14 | 1.00 | | | |
| Red meat fat | 0.45 | 0.48 | 0.40 | 0.50 | 0.20 | 0.92 | 1.00 | | |
| White meat fat | −0.10 | −0.10 | −0.07 | −0.09 | −0.08 | 0.41 | 0.08 | 1.00 | |
| Other source fat | 0.41 | 0.22 | 0.49 | 0.36 | 0.19 | 0.14 | 0.12 | 0.09 | 1.00 |

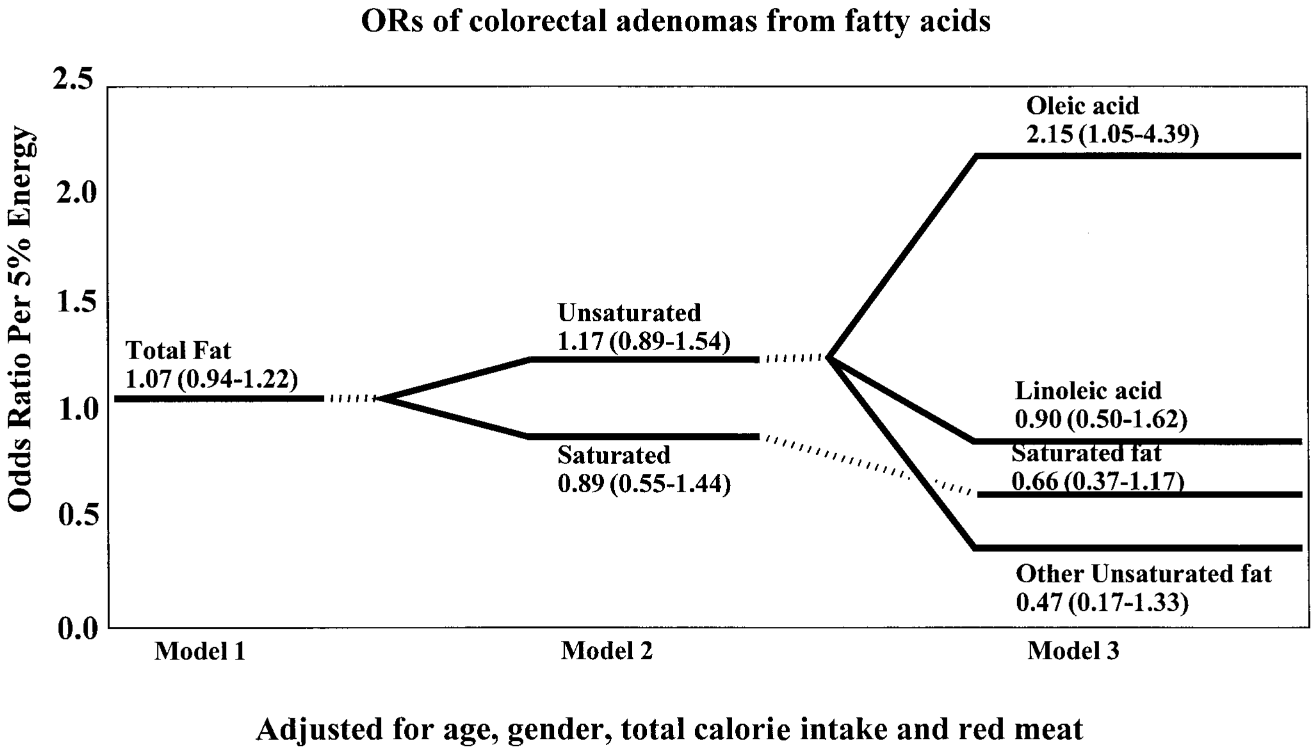


**FIGURE 1** – Association between total fat and different fatty acid intake and colorectal adenoma.

The ORs corresponding to both the sex-specific analysis and the combined analysis for all variables such as fat, fiber and fruits and vegetables and their subtypes (data not shown) had rather similar values. However, none of the associations were statistically significant except for the OR corresponding to oleic acid intake and the adenoma risk among males (OR: 2.50; 95% CI: 1.04–6.0).

## DISCUSSION

The present study relating to the development of colorectal adenomas focused on fat, fiber, fruits and vegetables and their various subtypes. A positive association was observed between the risk of adenomas and fat intake, particularly for the intake of oleic acid. A moderately strong inverse association was observed for adenoma risk and fiber intake. Higher intake of fruits and vegetables indicated an inverse, statistically nonsignificant association with the development of adenomas.

Several studies have suggested that diet plays a role in the etiology of colorectal adenomas. Some studies have reported that dietary fat was positively associated with colorectal adenomas.[4,5,7–9] The results of the present study also suggest an increase in the risk of colorectal adenoma associated with increasing intake of total fat, which persist although they are weaker after adjusting for red meat.

When we further investigated fat subtypes, unsaturated fat intake, especially oleic acid—the major monounsaturated fatty acid—was associated with an increased risk for colorectal adenomas. Only minimal data were available from other studies to evaluate the finding for subtypes of fat observed in the present study. However, 2 studies reported a positive association between oleic acid and risk for neoplasm. One was a prospective cohort study of postmenopausal women in the United States, which found a significant increased breast cancer risk for high intake of oleic acid.[19] In the other, Slattery *et al.*[20] found an increased risk of colon cancer with increasing consumption of monounsaturated fatty acids among women with a family history of colorectal cancer. The primary foods contributing to oleic acid intake in our study population were meat (24.1%), dairy products (18.1%), margarine (11.5%), biscuits, muffins, doughnuts and cookies (10.1%), and mayonnaise, salad oil and cooking oil (9.2%). A plausible hypothesis may be that oleic acid is a marker of unhealthy diet in the study population because several of the above

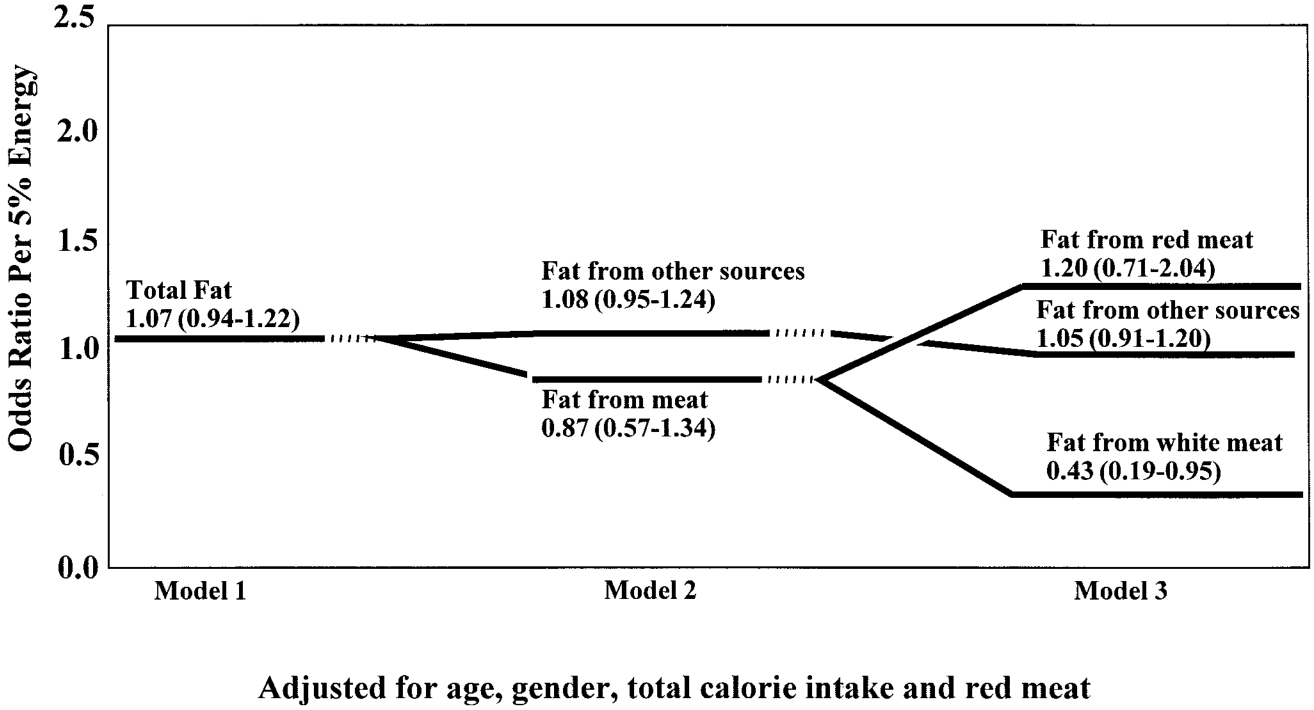


FIGURE 2 – Association between total fat and fat from different sources and colorectal adenoma.

foods such as margarine, mayonnaise and sweet baked food contain the hydrogenated fat, which is rich in *trans*-fatty acids and might be associated with an increased risk of colorectal neoplasia.[20–22]

In contrast, olive oil, in which the predominant fatty acid is oleic acid, showed a protective effect for breast cancer and might be inversely associated with colon cancer.[23] Olive oil is widely used in the Mediterranean diet, which is high in whole grains, fruits and vegetables and might also serve as proxy for a healthy diet. Therefore, it is also important to consider the underlying foods that contribute to the intake of the specific fat subtypes and modification of fat by food processing (hydrogenation), when comparing findings from different study populations with different diets. Furthermore, we noted that the various dietary fat subtypes were highly correlated. The difficulty in disentangling their independent association with colorectal adenomas results in less precise estimates (Table II). However, the high correlation does not explain the significant positive association between adenoma risk and oleic acid especially when compared with total fat intake.

Previous studies[4–6] have found that increased red meat intake was associated with a high risk for colorectal adenomas whereas high consumption of white meat was associated with a low risk of colorectal adenomas.[9,24] In the present study we observed only a weak positive association between red meat fat and colorectal adenomas. The attenuation of risk estimate for red meat fat after adjusting for red meat indicated that the previously observed association[6] between adenoma risk and red meat intake was mainly due to meat components other than fat. These other components of meat such as meat cooking practice[25] or preserved *vs.* processed meats[26] may be more important than fat from red meat in relation to colon adenoma risk.

Several studies have reported an inverse association between fiber intake and risk for adenomas.[7–10,27–31] However, there are other studies that show no clear association between dietary fiber and risk for adenomas,[32,33] and hence the evidence is not conclusive. Our finding of an inverse association supports the hypothesis that a high fiber diet can reduce the risk for colorectal adenomas as the fiber may bind to bile acids, reduce colonic transit time, increase stool bulk, ferment fatty acids that may be anticarcinogenic and reduce the conversion of primary to secondary bile acids by lowering stool pH.[34] A strong inverse association between fruit fiber and adenoma risk was also reported in other studies.[10,35] Fruit fiber in particular is high in pectin content, which is highly soluble and a fermentable fiber. The effect of fruit fiber might be due to the antiproliferative effect of short chain fatty acids produced by the gut flora.

The absence of strong associations between fruits and vegetables and colorectal adenomas in the study population contrasts with findings in various epidemiologic studies demonstrating that a diet rich in fruits and vegetables protects against the development of different types of cancer, including colon neoplasia.[10,36] In the present study the associations between fruits and vegetables and colorectal adenomas are consistent with findings of recent cohort studies,[37–39] which do not support the hypothesis that increased consumption of fruits and vegetables provides biologic plausibility for reduction in the incidence of colorectal cancers.[40] The commonly cited limitations of food frequency questionnaire, including the requirement of memory and quantitative skills on the part of the respondent, and the reporting of greater consumption of "healthier" foods, probably led to some degree of nondifferential misclassification of subjects for fruit and vegetable intake, and subsequently to attenuated risk.

The intake of foods (and hence macronutrients) can be different for men and women. Therefore, in addition to analyzing sex solely as a potential confounder, a sex-specific analysis that included sex as a potential confounder was also performed. However, the results did not show any difference in the risk.

The retrospective assessment of dietary intake in the present study has the potential for recall bias. However, as the cases had adenomas rather than cancer, it is less likely that dietary habits changed after diagnosis. For these reasons, we expect that their responses to questions about the usual dietary habits are less likely to be influenced by their disease. Another limitation of the study was that the cases were interviewed only after the treatment procedures were completed, which could have led to potential

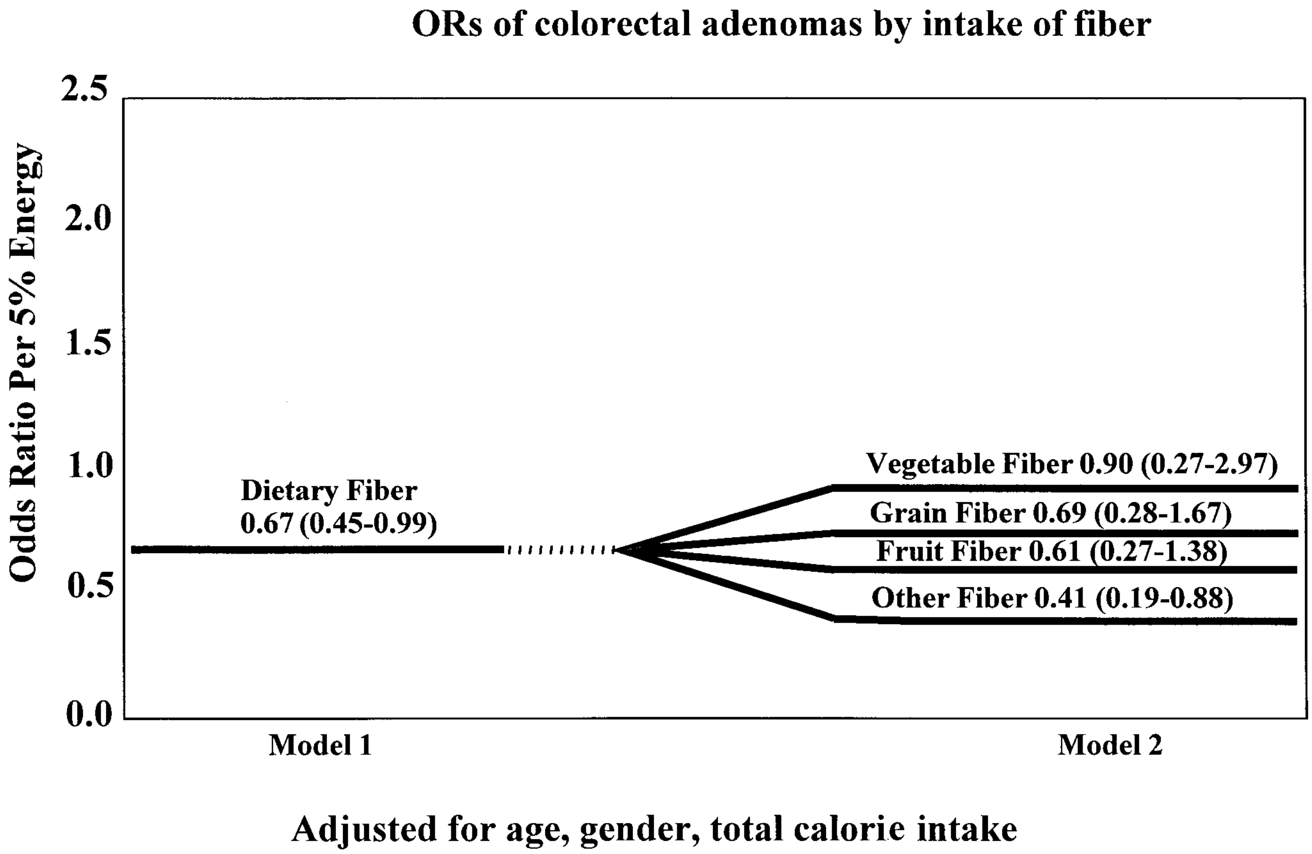


FIGURE 3 – Association between total fiber and different sources of fiber and colorectal adenoma.

TABLE III – ASSOCIATION BETWEEN FRUIT AND VEGETABLE INTAKE AND COLORECTAL ADENOMA; ODDS RATIO (OR) AND 95% CONFIDENCE INTERVAL (95% CI) PER 100 G/DAY INTAKE ADJUSTED FOR AGE, GENDER, AND TOTAL ENERGY

| Factors (100 gm/day)[1] | Distribution[1] | OR (95% CI) |
|---|---|---|
| All fruits/fruit juice | 235.3 (65.2, 499.2) | 0.92 (0.82–1.03) |
| Citrus fruits | 108.5 (14.2, 287.9) | 0.92 (0.78–1.08) |
| All vegetables | 165.6 (79.5, 295.7) | 0.83 (0.67–1.04) |
| Vegetables excluding mature beans | 152.0 (76.5, 284.0) | 0.85 (0.67–1.08) |
| Vegetables excluding starch-rich | 111.3 (41.4, 209.0) | 0.82 (0.62–1.07) |
| Cruciferous vegetables | 12.5 (1.4, 38.8) | 0.62 (0.23–1.72) |
| Yellow-orange vegetables | 11.9 (1.0, 35.0) | 0.90 (0.34–2.33) |
| Green-leafy vegetables | 69.7 (25.5, 126.5) | 0.72 (0.46–1.12) |
| Lycopene-rich vegetables | 15.2 (1.8, 52.4) | 0.51 (0.20–1.29) |
| All fruits + all vegetables[2] | 407.6 (186.3, 738.4) | 0.92 (0.84–1.00) |

[1]Median ($10^{th}$, $90^{th}$ percentiles) in control subjects only. –[2]All fruits: apple, applesauce, pears, banana, peach, plums, cantaloupe, watermelon, strawberries, orange, grapefruit, grapes, apricots, raisins, prunes, pineapple, fruit mix, jelly, jam, orange juice, apple juice, other fruit juice, fruit drinks.

Citrus fruits: oranges, grapefruits, orange juice and grapefruit juice.

All vegetables: string beans, green beans, peas, corn, squash, zucchini, broccoli, cauliflower, Brussel sprouts, spinach, mustard greens, turnip greens, collards, kale, Swiss chard, mixed vegetables, coleslaw, cabbage, sauerkraut, carrots, lettuce, green pepper, cucumber, celery, beets, tomatoes, canned tomatoes, tomato sauce, ketchup, salsa, red chili sauce, onions, garlic, potatoes prepared other ways, sweet potatoes, tofu soybeans, chili with beans, other beans, vegetable and tomato soups, tomato juice.

Vegetables excluding mature beans: all vegetables excluding chili with beans and other beans such as baked beans, pintos, kidney, limas and lentils from all vegetables.

Vegetables excluding starch-rich: all vegetables excluding peas, corn, sweet potatoes, yams, other potatoes, including boiled, baked, mashed and potato salad from vegetables excluding mature beans.

Cruciferous vegetables: broccoli, brussels sprouts, cauliflower, cole slaw, cabbage, sauerkraut, mustard green, turnip greens, collards, kale, chard.

Yellow-orange vegetables: winter squash like zucchini, baked squash, carrots and sweet potatoes.

Green-leafy vegetables: string beans, green beans, peas, broccoli, spinach, mustard green, turnip greens, collards, kale, chard and green salad.

Lycopene-rich vegetables: tomatoes and tomato juice.

recall bias. However, as noted above, fewer problems are likely to be posed when adenomas (compared with cancer) are studied.

Further limitations faced by the study include both selection bias and issues regarding participation rates: cases had a full colonoscopy, whereas controls had only a flexible sigmoidoscopy; and thus some controls might have had undetected adenomas. These undetected adenomas among the controls could tend to attenuate the results. Also the nonparticipation rates were slightly higher (10%) among controls than cases. In both groups this was largely due to subject refusal. The relatively small percentage difference in nonparticipation rates probably has a negligible effect on the results.

In summary, we observed increased colorectal adenoma risk with increased fat intake. The strong positive association between adenoma risk and intake of oleic acid is likely to be an indicator of "unhealthy" food intake. However, the relationship needs further exploration. An inverse association was observed between adenoma risk and fiber, particularly fruit and grain fiber.

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