



Dietary Fat and Fatty Acids and Risk of Colorectal Cancer in Women

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Received for publication February 11, 2004; accepted for publication June 22, 2004.

The authors examined the association of intakes of different types of fat and fatty acids with risk of colorectal cancer using data from the Women's Health Study, a randomized trial of low-dose aspirin and vitamin E carried out among 39,876 healthy US women aged ≥ 45 years. Among the 37,547 women eligible for the present study, 202 developed colorectal cancer during an average follow-up period of 8.7 years (1993–2003). Intakes of dietary fat and its food sources were assessed at baseline by food frequency questionnaire. Cox proportional hazards regression was used to estimate relative risks and 95% confidence intervals. Total fat intake was not related to colorectal cancer risk, nor were intakes of the different types of fat and major fatty acids. However, the authors observed a positive association between intake of fried foods away from home and colorectal cancer risk (highest quintile vs. lowest: relative risk = 1.86, 95% confidence interval: 1.09, 3.16; p for trend = 0.01). **These prospective cohort data provide little support for an association between dietary fat and colorectal cancer risk.** However, intake of fried foods and/or other factors related to their intake may be associated with colorectal cancer development. This finding warrants further examination.

colorectal neoplasms; dietary fats; fatty acids; women

Abbreviation: CI, confidence interval.

Dietary fat has been hypothesized to increase the risk of colorectal cancer—partly by increasing secretion of bile acids, which have a nonspecific irritant effect on the colonic lumen, thereby damaging the colonic mucosa, stimulating regeneration of the epithelium, and ultimately increasing the risk of endogenous mutation (1–4). Dietary fat may also influence colorectal cancer risk through its involvement in insulin resistance, altered immunologic responses, and changes in the fatty acid composition of the membranes (5).

Although ecologic comparisons and animal studies support a positive association between intake of dietary fat and risk of colorectal cancer (6–10), findings from most epidemiologic studies of dietary fat and colorectal cancer risk have been inconclusive. A pooled analysis of results from 13 case-control studies found no association between dietary fat intake and colorectal cancer risk (11). Among the five prospective cohort studies (12–16) with a comprehensive assessment of diet, four (13–16) did not find clear

evidence of an association. Studies evaluating individual types of fat in relation to colorectal cancer risk have also yielded mixed findings. A positive association between saturated fat intake and colorectal cancer risk was observed in some studies (12, 17–20) but not in others (13–16, 21–27). Two studies observed a positive association between dietary intake of polyunsaturated fat and risk of colorectal cancer (25, 28), while most other studies found a null association (13, 14, 16, 27). Moreover, very few studies have comprehensively examined the association with individual dietary fatty acids (29, 30), which may better characterize the specific effects of dietary fat on development of colorectal cancer.

To gain a better understanding of the relation of fat intake to colorectal cancer, we conducted detailed analyses of intakes of total fat, individual types of fat, and specific fatty acids in a large cohort of female health professionals. We

additionally investigated the risk of colorectal cancer associated with fat from various food sources.

MATERIALS AND METHODS

Study cohort

The Women's Health Study is an ongoing randomized, double-blind, placebo-controlled 2×2 factorial trial evaluating the use of low-dose aspirin and vitamin E for the primary prevention of cancer and cardiovascular disease in US women (31). Beginning in 1993, a total of 39,876 female health professionals aged ≥ 45 years who were free of heart disease and cancer (except nonmelanoma skin cancer) were randomly assigned to the trial. In the present study, we excluded 2,329 women who provided insufficient dietary information at baseline, had an implausible total energy intake (< 600 kcal/day or $\geq 3,500$ kcal/day), or did not have information on potential risk factors at study entry. These exclusions gave us a total of 37,547 women who were eligible for analysis.

Dietary assessment

At baseline, participants completed a 131-item food frequency questionnaire. On the questionnaire, women were asked to indicate their average consumption over the previous year of various types of food, specifying units or portion size, by selecting one of nine possible responses ranging from "never or less than once per month" to "six or more times per day." We calculated individual nutrient intakes by multiplying the frequency of each food consumed by the nutrient content of the specified portion and taking into account the types of fat or oil used for preparation. Values for fat, fatty acids, and other nutrients in the foods were obtained from US Department of Agriculture sources (32), supplemented with information obtained from the manufacturers. The n-6 polyunsaturated fat data reported in the present study were based on 18:2 and 20:4 fatty acids. The data on n-3 polyunsaturated fat included 20:5 and 22:6 fatty acids. Total amounts of *trans* isomers of unsaturated fat were estimated on the basis of methods proposed by Sacks and Willett (33). We included *trans* isomers of 18-carbon (*t*18:1 and *t*18:2) and 16-carbon (*t*16:1) unsaturated fatty acids. Intakes of dietary fat and fatty acids were adjusted for total energy by means of the multivariate nutrient density method, in which nutrient intake was expressed as a percentage of total energy and analyzed in the model with inclusion of total energy intake (34).

We examined food sources of animal fat, including red meat (beef or lamb as a main dish, beef, pork, or lamb in a sandwich, hot dogs, bacon, processed meats, and hamburgers), white meat (chicken and turkey, with and without skin), fish and other seafood (fish, canned tuna, and shrimp), processed meat (hot dogs, processed meats, and bacon), high-fat dairy products (whole milk, cream, sour cream, ice cream, cream cheese, hard cheese, and butter), and low-fat dairy products (skim or low-fat milk, yogurt, cottage or ricotta cheese, sherbet, ice milk, and frozen yogurt). We also evaluated major food contributors to vege-

table fat in this cohort, including mayonnaise and creamy salad dressing, margarine, oily salad dressing (olive oil dressing, other oil-and-vinegar dressing), nuts (peanut butter, peanuts, and other nuts), fried foods eaten away from home (French fries, fried chicken, fried fish), and baked products (ready-made sweet roll, coffee cake, or other pastry; doughnuts; crackers; and ready-made cookies).

The reliability and validity of fat intakes based on the food frequency questionnaire had been previously investigated in the Nurses' Health Study, which enrolled a cohort of female nurses with profiles similar to those of participants in the present study. Pearson correlation coefficients for correlations between energy-adjusted intake of each type of fat from the 1980 food frequency questionnaire and intake from two 1-week dietary records ranged from 0.48 to 0.73 (35, 36). Intake of dietary fat based on the food frequency questionnaire correlated reasonably well with the fatty acid composition of adipose tissue (Spearman's $r = 0.51$ for *trans* unsaturated fat; Spearman's $r = 0.48$ for n-3 polyunsaturated fat) (35). The reliability and validity of data on dietary meat and dairy products had also been evaluated in the Nurses' Health Study; correlation coefficients were 0.5 or greater for most food items (37).

Ascertainment of colorectal cancer cases

On follow-up questionnaires mailed every 6 months during the first year and annually thereafter, participants were asked to provide information on whether they had been diagnosed with colorectal cancer. For women who reported a diagnosis of colorectal cancer and for those who died during the trial, we sought permission to obtain relevant medical records and pathology reports. An endpoint committee composed of physicians reviewed and confirmed medical diagnoses and extracted information on anatomic location, neoplastic behavior, and histologic grade. During an average follow-up period of 8.7 years (1993–2003), 202 colorectal cancer cases were confirmed among the women in the present study. Of these case women, 83 had a primary tumor in the proximal colon and 75 had a primary tumor in the distal colon. Forty case women had a primary tumor in the rectum, and the remaining four case women had tumors whose location could not be narrowed down to the proximal or distal colon. The mean age at diagnosis of colorectal cancer was 64 years (range, 47–88 years).

Statistical analysis

Intakes of dietary fat and fatty acids, as well as intakes of food from various food groups, were categorized into quintiles on the basis of the overall distribution of nutrient intakes in all women. We compared the age-adjusted baseline distribution of risk factors for colorectal cancer according to quintiles of each type of fat. Proportions were tested with the stratified Cochran-Mantel-Haenszel test, and mean values were compared using multiple linear regression.

Cox proportional hazards analysis was used to estimate relative risks and 95 percent confidence intervals for colorectal cancer, comparing the incidence rate for a given

quintile of intake with the lowest quintile. Data in the multivariate model were adjusted for age (in years), random treatment assignment (aspirin vs. placebo, vitamin E vs. placebo), body mass index (weight (kg)/height (m)²: <23, 23–24.9, 25–26.9, 27–29.9, ≥30), family history of colorectal cancer (yes, no), self-reported colorectal polyps (yes, no), physical activity (energy expenditure (kcal/week), in quartiles), cigarette smoking (never, past, current), alcohol consumption (total daily intake: none, <15 g, ≥15 g), use of postmenopausal hormone therapy (never, past, current), and total energy intake (kcal/day, in quintiles). We conducted tests for trend by fitting the median nutrient value in each quintile to create a continuous variable. All *p* values were two sided.

RESULTS

Table 1 presents the baseline distribution of data on risk factors for colorectal cancer by intakes of saturated, monounsaturated, n-6 polyunsaturated, and *trans* unsaturated fat. Women with higher intakes of the four types of fat tended to be heavier and less active and consumed less alcohol. They also tended to be current smokers. With the exception of n-6 polyunsaturated fat, women with higher intakes of the various types of fat were less likely to be using postmenopausal hormone therapy. Values for a history of colorectal polyps did not differ across quintiles of fat intake.

Table 2 presents the multivariate relative risks for colorectal cancer according to quintiles of total fat and types of fat. Intake of total fat was unrelated to risk of colorectal cancer (*p* for trend = 0.64). Intakes of various types of fat and cholesterol were also not significantly associated with colorectal cancer (table 2). When we additionally adjusted for other types of fat and cholesterol in the model, the relative risks for *trans* fat intake became stronger (highest quintile vs. lowest: relative risk = 1.59, 95 percent confidence interval (CI): 0.94, 2.70; *p* for trend = 0.06). Results for other types of fat were not appreciably changed (data not shown).

We further estimated the associations between intakes of specific fatty acids and risk of colorectal cancer (table 3). Intakes of short-, median-, and long-chain saturated fatty acids (4:0–18:0) were not associated with risk of colorectal cancer. However, intake of 16:1 monounsaturated fatty acid was inversely associated with risk of colorectal cancer; the multivariate relative risk for the highest quintile of intake relative to the lowest was 0.67 (95 percent CI: 0.42, 1.08; *p* for trend = 0.05). Intakes of n-6, n-3, and *trans* unsaturated fatty acids were not significantly associated with colorectal cancer risk (table 3). Additional adjustment for other types of fat and cholesterol in the model did not materially change the results for intakes of most fatty acids, except that the relative risks for *t*18:1 and *t*18:2 fatty acids became stronger. The relative risks for the highest quintile of intake relative to the lowest were 1.94 (95 percent CI: 0.92, 2.58; *p* for trend = 0.08) for *t*18:1 fatty acid and 1.58 (95 percent CI: 0.94, 2.67; *p* for trend = 0.09) for *t*18:2 fatty acid.

We also evaluated major food sources of animal fat and vegetable fat in relation to risk of colorectal cancer (table 4). Intakes of food sources of animal fat, including processed meat, white meat, fish or other seafood, and dairy products,

TABLE 1. Age-adjusted (in 5-year categories) baseline data on demographic characteristics and colorectal cancer risk factors according to quintile of various types of dietary fat, Women's Health Study, 1993–2003

Characteristic	Saturated fat					Monounsaturated fat					n-6 polyunsaturated fat					Trans unsaturated fat				
	Q*1	Q3	Q5	<i>P</i> _{trend}	Q1	Q3	Q5	<i>P</i> _{trend}	Q1	Q3	Q5	<i>P</i> _{trend}	Q1	Q3	Q5	<i>P</i> _{trend}	Q1	Q3	Q5	<i>P</i> _{trend}
No. of participants	7,510	7,510	7,509		7,510	7,510	7,509		7,510	7,510	7,509		7,510	7,510	7,509		7,510	7,510	7,509	
Mean age (years)	54.7	53.9	53.1	<10 ⁻⁴	54.3	53.8	53.5	<10 ⁻⁴	53.8	54.0	54.3	<10 ⁻⁴	54.7	54.1	53.1	<10 ⁻⁴	54.7	54.1	53.1	<10 ⁻⁴
Mean body mass index†	24.8	26.0	27.0	<10 ⁻⁴	25.0	26.1	27.0	<10 ⁻⁴	25.5	26.1	26.4	<10 ⁻⁴	25.0	26.0	27.0	<10 ⁻⁴	25.0	26.0	27.0	<10 ⁻⁴
Current smoking (%)	7.4	11.0	22.4	<10 ⁻⁴	7.4	11.7	21.2	<10 ⁻⁴	11.7	12.5	15.7	<10 ⁻⁴	7.7	12.9	18.0	<10 ⁻⁴	7.7	12.9	18.0	<10 ⁻⁴
Current use of postmenopausal hormone therapy (%)	44.7	43.4	37.5	<10 ⁻⁴	43.6	43.0	38.3	<10 ⁻⁴	42.0	42.2	42.1	<10 ⁻⁴	44.3	42.3	40.4	<10 ⁻⁴	44.3	42.3	40.4	<10 ⁻⁴
Mean total energy intake (kcal/day)	1,678	1,749	1,742	<10 ⁻⁴	1,657	1,742	1,768	<10 ⁻⁴	1,658	1,753	1,751	<10 ⁻⁴	1,711	1,720	1,741	<10 ⁻⁴	1,711	1,720	1,741	<10 ⁻⁴
Mean total alcohol consumption (g/day)	4.8	4.1	3.4	<10 ⁻⁴	4.4	4.3	3.5	<10 ⁻⁴	5.0	4.0	3.7	<10 ⁻⁴	5.0	4.2	2.9	<10 ⁻⁴	5.0	4.2	2.9	<10 ⁻⁴
Mean physical activity (kcal/week)	1,335	936	718	<10 ⁻⁴	1,345	918	702	<10 ⁻⁴	1,148	945	853	<10 ⁻⁴	1,379	907	687	<10 ⁻⁴	1,379	907	687	<10 ⁻⁴
Family history of colorectal cancer (%)	9.6	10.6	10.0	0.19	9.5	10.8	10.8	<0.01	9.7	10.5	10.5	0.113	9.9	10.4	11.1	<0.01	9.9	10.4	11.1	<0.01
History of colon/rectal polyps (%)	2.5	2.7	2.8	0.67	2.5	2.3	2.7	0.37	2.3	2.7	2.7	0.09	2.6	2.5	2.3	0.09	2.6	2.5	2.3	0.82

* Q, quintile.
 † Weight (kg)/height (m)².
 ‡ A history of colorectal cancer in a first-degree relative.

TABLE 2. Relative risk* of colorectal cancer according to quintile of baseline intake of total fat and various types of fat, Women's Health Study, 1993–2003

	Quintile of intake					P_{trend}
	1	2	3	4	5	
Total fat						
Median (% energy)	22	27	30	33	38	
No. of cases	40	49	39	37	37	
Relative risk	1.00†	1.24	0.99	0.95	1.00	0.64
95% CI‡		0.81, 1.86	0.63, 1.54	0.61, 1.58	0.63, 1.58	
Animal fat						
Median (% energy)	10	14	16	18	23	
No. of cases	48	50	32	35	37	
Relative risk	1.00†	1.04	0.72	0.78	0.83	0.22
95% CI		0.70, 1.55	0.45, 1.13	0.50, 1.21	0.53, 1.29	
Vegetable fat						
Median (% energy)	9	11	13	16	19	
No. of cases	30	48	36	44	44	
Relative risk	1.00†	1.60	1.23	1.49	1.46	0.23
95% CI		1.01, 2.53	0.75, 1.99	0.94, 2.38	0.92, 2.33	
Saturated fat						
Median (% energy)	7	9	10	11	13	
No. of cases	52	39	41	27	43	
Relative risk	1.00†	0.76	0.83	0.55	0.92	0.44
95% CI		0.50, 1.15	0.55, 1.25	0.35, 0.89	0.61, 1.41	
Monounsaturated fat						
Median (% energy)	8	10	11	13	15	
No. of cases	38	54	36	36	38	
Relative risk	1.00†	1.45	0.98	0.99	1.09	0.72
95% CI		0.96, 2.20	0.62, 1.56	0.62, 1.57	0.68, 1.73	
n-6 polyunsaturated fat						
Median (% energy)	3.8	4.7	5.4	6.2	7.6	
No. of cases	26	48	37	47	44	
Relative risk	1.00†	1.83	1.41	1.78	1.60	0.16
95% CI		1.13, 2.95	0.85, 2.34	1.10, 2.88	0.98, 2.60	
n-3 polyunsaturated fat						
Median (% energy)	0.03	0.06	0.08	0.13	0.21	
No. of cases	42	36	37	39	48	
Relative risk	1.00†	0.88	0.89	0.92	1.11	0.43
95% CI		0.56, 1.37	0.57, 1.39	0.59, 1.43	0.73, 1.69	
Trans unsaturated fat						
Median (% energy)	0.6	0.9	1.1	1.4	1.9	
No. of cases	42	36	43	33	48	
Relative risk	1.00†	0.92	1.08	0.86	1.30	0.18
95% CI		0.59, 1.44	0.72, 1.69	0.55, 1.40	0.89, 2.05	
Dietary cholesterol						
Median (mg/1,000 kcal)	85	109	127	147	181	
No. of cases	48	46	33	39	36	
Relative risk	1.00†	1.00	0.76	0.88	0.79	0.23
95% CI		0.67, 1.51	0.49, 1.18	0.57, 1.35	0.51, 1.22	

* Adjusted for age, random treatment assignment, body mass index, family history of colorectal cancer, history of colorectal polyps, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone therapy, and total energy intake in a multivariate model.

† Referent.

‡ CI, confidence interval.

were not significantly associated with colorectal cancer risk. However, intake of red meat was inversely associated with risk of colorectal cancer; the relative risk for the highest quintile relative to the lowest was 0.66 (95 percent CI: 0.40, 1.09; p for trend = 0.05). Additional adjustment for saturated, monounsaturated, n-6 and n-3 polyunsaturated, and *trans* unsaturated fat and cholesterol in the model did not attenuate the relative risks for red meat intake, although the dose-response trend became nonsignificant ($p = 0.15$). When we examined food sources of vegetable fat, we observed an increased risk with increasing intake of fried foods prepared away from home; the relative risk comparing the highest quintile with the lowest was 1.86 (95 percent CI: 1.09, 3.16; p for trend = 0.01). Additional adjustment for types of fat and cholesterol did not attenuate the relative risks for fried food intake, and the trend remained significant ($p = 0.004$). Intakes of other food sources of vegetable fat were not significantly associated with colorectal cancer risk (table 4).

Because methods of cooking meat have been hypothesized to be related to risk of colorectal cancer (38, 39), we examined the doneness of beef or lamb as a main dish in relation to colorectal cancer risk. In comparison with meat cooked rare and medium-rare, the relative risks were 0.73 (95 percent CI: 0.47, 1.11) for meat cooked medium, 1.02 (95 percent CI: 0.68, 1.52) for meat cooked medium well, and 0.94 (95 percent CI: 0.63, 1.41) for meat cooked well done (p for trend = 0.83).

Since different underlying etiologies have been proposed for cancers of the proximal colon and cancers of the distal colon (40–42), we examined whether the overall risk associated with intakes of total fat and types of fat was specific to either tumor site. Intakes of dietary fat and individual types of fat were not significantly associated with either tumor site (data not shown).

DISCUSSION

In the present prospective study, total fat intake was not associated with colorectal cancer risk. In addition, intakes of saturated fat, monounsaturated fat, n-6 polyunsaturated fat, n-3 polyunsaturated fat, and *trans* unsaturated fat were not significantly associated with risk of colorectal cancer. Intakes of 16:1 monounsaturated fatty acid and red meat were associated with colorectal cancer risk in an unexpected direction. However, a positive association was observed between intake of fried foods away from home and risk of colorectal cancer.

Consistent with most other prospective cohort studies (13–16, 25), our results suggest that intake of total fat is not associated with risk of colorectal cancer. In the meta-analysis that pooled 13 case-control studies, Howe et al. (11) also found a null association; the relative risk for the highest quintile relative to the lowest was 0.92 (95 percent CI: 0.77, 1.10; p for trend = 0.67). The lack of a positive association was also evident in the present study and in most other large cohort studies (13–16, 25) for intakes of animal fat and its two major components, saturated fat and monounsaturated fat. However, the Nurses' Health Study investigators did find a twofold increased risk of colon cancer (relative risk =

1.89, 95 percent CI: 1.13, 3.15; p for trend = 0.01) among women in the highest quintile of animal fat intake compared with those in the lowest quintile (12). Since the Nurses' Health Study cohort was relatively younger (aged 34–59 years) than most other cohorts, including ours, it is possible that age may modify the association. As is shown by the meta-analysis finding, age clearly modified the association in women; an increased risk was found with higher intake of animal fat in women aged <50 years but not in those aged ≥50 years (11). Although we found no difference in risk by age in our cohort, more studies of modification of the effect by age, with larger numbers of cases, are warranted.

The major food source of animal fat in our study was red meat. Although the Nurses' Health Study (12), along with three other cohort studies (13, 43, 44), found an increased risk of colon cancer with higher intake of red meat, other studies failed to observe the association (15, 16, 25, 26, 45–50). Likewise, we and Hirayama (51), in a Japanese cohort study, reported a lower risk with higher red meat consumption, although our finding needs to be interpreted with caution because of the limited number of cases in our data. Given our finding of no change in the relative risks for red meat intake after additional adjustment for all types of fat and cholesterol, it is likely that the inverse association with red meat intake in our cohort may be attributable to factors other than fat content (5, 52). One nonfat component of meat, 4:0 short-chain fatty acid, which is produced in the colon through fermentation of dietary fiber, has been linked to reduction of colorectal cancer risk (53). However, our data offered little support for this hypothesis. It has also been suggested that heterocyclic amines or polycyclic aromatic hydrocarbons, mutagenic chemicals induced by cooking meat at high temperature or for a long time, may increase risk of colorectal cancer (38, 39). Our study, along with a Swedish case-control study (54), did not find an association between the doneness of red meat and colorectal cancer risk, although our results may be incomplete, since we only had information on doneness for one food item (beef or lamb as a main dish). Finally, other dietary factors have been hypothesized to modify the effect of red meat consumption on colorectal cancer risk (55, 56). In two cohort studies, higher intakes of legumes and green-yellow vegetables modified the association between red meat intake and colorectal cancer risk (44, 51), but our power to test this hypothesis is currently limited. In a recent meta-analysis of red meat intake comprising 17 prospective studies, the combined odds ratio was only slightly greater than 1 (odds ratio = 1.17, 95 percent CI: 1.05, 1.31) for a 100-g/day (approximately one half serving) increase in red meat intake (56), which suggests that the risk of colorectal cancer associated with red meat intake may not be as high as previously thought.

The role of dietary 16:1 monounsaturated fatty acid, which is abundant in both red meat and white meat, in cancer development is unknown. In our data, intake of 16:1 fatty acid was inversely associated with colorectal cancer risk, although other two case-control studies observed a null association (29, 30). Findings from two European studies which tested the relation between tissue stores of 16:1 fatty acid and breast cancer risk were not consistent (57, 58). Given that intake of 16:1 fatty acid only accounts for a small proportion

TABLE 3. Relative risk* of colorectal cancer according to quintile of baseline intake of specific fatty acids, Women's Health Study, 1993–2003

	Quintile of intake					<i>P</i> _{trend}
	1	2	3	4	5	
<i>Saturated fat</i>						
4:0 (butyric)						
Median (% energy)	0.08	0.13	0.17	0.21	0.29	
No. of cases	36	45	39	40	42	
Relative risk	1.00†	1.28	1.10	1.16	1.19	0.66
95% CI‡		0.83, 1.99	0.69, 1.74	0.73, 1.82	0.76, 1.86	
6:0–10:0§						
Median (% energy)	0.15	0.22	0.28	0.35	0.48	
No. of cases	34	52	40	36	40	
Relative risk	1.00†	1.57	1.20	1.10	1.22	0.98
95% CI		1.01, 2.41	0.76, 1.91	0.61, 1.76	0.77, 1.93	
12:0 + 14:0¶						
Median (% energy)	0.64	0.86	1.03	1.23	1.63	
No. of cases	46	45	40	30	41	
Relative risk	1.00†	1.01	0.94	0.71	0.99	0.65
95% CI		0.67, 1.53	0.61, 1.43	0.45, 1.13	0.65, 1.52	
16:0 (palmitic)						
Median (% energy)	4.1	5.1	5.7	6.4	7.5	
No. of cases	45	45	37	36	39	
Relative risk	1.00†	1.02	0.87	0.87	0.99	0.76
95% CI		0.67, 1.54	0.56, 1.35	0.56, 1.36	0.63, 1.55	
18:0 (stearic)						
Median (% energy)	1.7	2.2	2.6	2.9	3.5	
No. of cases	48	38	47	31	38	
Relative risk	1.00†	0.86	1.01	0.69	0.87	0.41
95% CI		0.53, 1.24	0.67, 1.53	0.43, 1.09	0.56, 1.35	
<i>Monounsaturated fat</i>						
16:1 (palmitoleic)						
Median (% energy)	0.4	0.5	0.6	0.7	0.8	
No. of cases	48	54	31	40	29	
Relative risk	1.00†	1.16	0.69	0.90	0.67	0.05
95% CI		0.78, 1.72	0.47, 1.09	0.59, 1.38	0.42, 1.08	
18:1 (oleic)						
Median (% energy)	7	9	10	11	13	
No. of cases	37	56	39	30	40	
Relative risk	1.00†	1.54	1.09	0.84	1.16	0.67
95% CI		1.02, 2.34	0.69, 1.72	0.51, 1.37	0.74, 1.84	
20:1 (gadoleic)						
Median (% energy)	0.04	0.06	0.07	0.09	0.12	
No. of cases	34	52	50	30	36	
Relative risk	1.00†	1.61	1.54	0.91	1.04	0.27
95% CI		1.05, 2.49	1.00, 2.39	0.55, 1.49	0.65, 1.67	

Table continues

of total energy intake in our cohort, the significant association is probably attributable to other components that are highly correlated with intake of 16:1 fatty acid. We also cannot rule out the possibility that our present finding may be due to chance, since so many comparisons were made.

In our data, intakes of vegetable fat and its major component, n-6 polyunsaturated fat, were not significantly associated with risk of colorectal cancer. Similarly, most other cohort studies reported a null association with either intake of vegetable fat or intake of polyunsaturated fat (12–15).

TABLE 3. Continued

	Quintile of intake					<i>P</i> _{trend}
	1	2	3	4	5	
<i>n-6 polyunsaturated fat</i>						
<i>18:2 (linoleic)</i>						
Median (% energy)	3.3	4.2	4.8	5.5	6.6	
No. of cases	27	44	40	51	40	
Relative risk	1.00†	1.63	1.48	1.88	1.42	0.21
95% CI		1.01, 2.64	0.91, 2.42	1.18, 3.00	0.87, 2.32	
<i>20:4 (arachidonic)</i>						
Median (% energy)	0.04	0.06	0.07	0.09	0.12	
No. of cases	49	40	38	33	42	
Relative risk	1.00†	0.86	0.84	0.73	0.90	0.55
95% CI		0.57, 1.32	0.55, 1.28	0.47, 1.14	0.59, 1.36	
<i>n-3 polyunsaturated fat</i>						
<i>20:5 (timnodonic)</i>						
Median (% energy)	<0.01	0.01	0.02	0.04	0.07	
No. of cases	45	35	40	45	37	
Relative risk	1.00†	0.79	0.89	0.99	0.79	0.61
95% CI		0.51, 1.23	0.58, 1.36	0.65, 1.51	0.51, 1.24	
<i>22:6 (cervonic)</i>						
Median (% energy)	0.02	0.04	0.06	0.09	0.14	
No. of cases	42	39	35	39	47	
Relative risk	1.00†	0.96	0.85	0.92	1.09	0.61
95% CI		0.62, 1.49	0.54, 1.33	0.59, 1.43	0.71, 1.66	
<i>Trans unsaturated fat</i>						
<i>t16:1</i>						
Median (% energy)	0.05	0.06	0.07	0.08	0.10	
No. of cases	49	49	31	38	35	
Relative risk	1.00†	1.03	0.68	0.85	0.80	0.22
95% CI		0.69, 1.54	0.43, 1.07	0.56, 1.32	0.51, 1.25	
<i>t18:1 (elaidic)</i>						
Median (% energy)	0.5	0.7	0.9	1.2	1.7	
No. of cases	42	36	44	32	48	
Relative risk	1.00†	0.92	1.12	0.85	1.33	0.20
95% CI		0.59, 1.44	0.73, 1.72	0.53, 1.35	0.87, 2.05	
<i>t18:2</i>						
Median (% energy)	0.03	0.04	0.05	0.07	0.09	
No. of cases	42	35	45	34	46	
Relative risk	1.00†	0.89	1.19	0.89	1.29	0.24
95% CI		0.57, 1.40	0.78, 1.82	0.56, 1.41	0.84, 1.98	

* Adjusted for age, random treatment assignment, body mass index, family history of colorectal cancer, history of colorectal polyps, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone therapy, and total energy intake in a multivariate model.

† Referent.

‡ CI, confidence interval.

§ Short- to medium-chain saturated fatty acids (6:0–10:0) include 6:0 (caproic), 8:0 (caprylic), and 10:0 (capric) fatty acids.

¶ The 12:0 (lauric) and 14:0 (myristic) fatty acids were combined because of low dietary intakes.

Experimental findings on the role of n-6 polyunsaturated fat in colorectal carcinogenesis are inconsistent. In vivo studies have suggested that n-6 fatty acids such as 18:2 n-6 fatty acid

might promote colonic cell proliferation, possibly through the protein kinase C pathway (59, 60). Conversely, a recent in vitro study found that 18:2 n-6 fatty acid had no effect on

TABLE 4. Relative risk* of colorectal cancer according to quintile of baseline intake of various food items, Women's Health Study, 1993–2003

	Quintile of intake					<i>P</i> _{trend}
	1	2	3	4	5	
<i>Food contributors to animal fat</i>						
Red meat						
Median (servings/day)	0.13	0.40	0.62	0.91	1.42	
No. of cases	49	48	39	36	30	
Relative risk	1.00†	1.10	0.93	0.81	0.66	0.05
95% CI‡		0.74, 1.65	0.61, 1.44	0.52, 1.28	0.40, 1.09	
White meat						
Median (servings/day)	0.13	0.21	0.43	0.56	0.86	
No. of cases	46	50	39	24	43	
Relative risk	1.00†	1.09	0.87	1.08	1.17	0.57
95% CI		0.73, 1.64	0.56, 1.34	0.65, 1.80	0.75, 1.83	
Processed meat						
Median (servings/day)	0	0.07	0.13	0.21	0.50	
No. of cases	51	45	42	32	32	
Relative risk	1.00†	1.18	1.27	0.95	0.85	0.25
95% CI		0.79, 1.77	0.84, 1.91	0.60, 1.49	0.53, 1.35	
Fish and other seafood						
Median (servings/day)	0.07	0.13	0.20	0.28	0.56	
No. of cases	43	47	31	36	45	
Relative risk	1.00†	1.26	0.79	1.05	1.23	0.40
95% CI		0.83, 1.90	0.50, 1.27	0.66, 1.65	0.77, 1.91	
Low-fat dairy products						
Median (servings/day)	0.13	0.50	1.00	1.42	2.71	
No. of cases	42	38	43	34	45	
Relative risk	1.00†	0.99	0.99	0.78	1.02	0.98
95% CI		0.63, 1.53	0.64, 1.53	0.49, 1.24	0.65, 1.59	
High-fat dairy products						
Median (servings/day)	0.13	0.28	0.56	0.92	1.86	
No. of cases	45	42	41	38	36	
Relative risk	1.00†	1.10	1.09	1.10	0.98	0.78
95% CI		0.72, 1.67	0.71, 1.68	0.70, 1.72	0.65, 1.59	

Table continues

the growth of colon cancer cells but 20:4 n-6 fatty acid may be important for tumor growth inhibition (61). In our cohort, intakes of 18:2 and 20:4 fatty acid were not significantly associated with colorectal cancer incidence. Two other case-control studies observed no association with intake of 18:2 fatty acid (29, 30), but one study reported a twofold increased risk in the highest quartile of 20:4 fatty acid intake (30). Clearly, the mechanism of n-6 polyunsaturated fat involved in incident colorectal cancer is complex, and more studies assessing individual n-6 fatty acids may help unravel its specific effects on cancer development.

One food source of vegetable fat, fried foods eaten away from home (such as French fries, fried chicken, and fried fish), was positively associated with risk of colorectal cancer in our cohort, which is consistent with results from two other studies (62, 63). The *trans* fat in fried foods, produced by

partial hydrogenation of polyunsaturated vegetable oil, may contribute to the positive association. It has been hypothesized that intake of *trans* fat may increase cancer development through disruption of the phospholipid cell membrane and associated enzymes and receptors (64, 65). Although the association of *trans* unsaturated fat with risk of colorectal cancer is not entirely clear in our data, one (66) of two case-control studies (66, 67) observed an increased risk of colon cancer in women with a higher intake of *trans* unsaturated fat. The presence of acrylamide, a mutagenic chemical, in the brown surface of many heated food products (68) is another likely explanation for the association. However, intake of baked products, another potential food source of acrylamide, was not positively associated with risk in our data, which is consistent with a case-control study that found no positive association between dietary acrylamide and

TABLE 4. Continued

	Quintile of intake					P_{trend}
	1	2	3	4	5	
<i>Food contributors to vegetable fat</i>						
<i>Mayonnaise or other creamy salad dressing§</i>						
Median (servings/day)	0.07		0.14		0.43	
No. of cases	78		55		68	
Relative risk	1.00†		1.19		1.18	0.37
95% CI			0.84, 1.68		0.84, 1.66	
<i>Margarine</i>						
Median (servings/day)	0	0.14	0.43	1.00	2.50	
No. of cases	59	42	18	43	38	
Relative risk	1.00†	0.68	0.79	1.14	1.18	0.07
95% CI		0.46, 1.02	0.46, 1.34	0.77, 1.70	0.77, 1.80	
<i>Oily salad dressing</i>						
Median (servings/day)	0	0.07	0.14	0.43	0.86	
No. of cases	41	41	28	66	26	
Relative risk	1.00†	0.98	1.23	1.69	0.96	0.52
95% CI		0.63, 1.51	0.76, 1.99	1.13, 2.52	0.57, 1.59	
<i>Nuts</i>						
Median (servings/day)	0	0.07	0.13	0.28	0.64	
No. of cases	100	34	47	37	42	
Relative risk	1.00†	0.83	1.00	0.95	1.05	0.61
95% CI		0.53, 1.30	0.66, 1.52	0.60, 1.49	0.67, 1.64	
<i>Fried foods eaten away from home¶</i>						
Median (servings/day)	0		0.07		0.29	
No. of cases	23		132		45	
Relative risk	1.00†		1.25		1.86	0.01
95% CI			0.80, 1.95		1.09, 3.16	
<i>Baked products</i>						
Median (servings/day)	0.07	0.27	0.43	0.78	1.50	
No. of cases	60	35	35	36	36	
Relative risk	1.00†	0.90	0.86	0.78	0.73	0.16
95% CI		0.59, 1.39	0.56, 1.31	0.51, 1.19	0.47, 1.14	

* Adjusted for age, random treatment assignment, body mass index, family history of colorectal cancer, history of colorectal polyps, physical activity, cigarette smoking, alcohol consumption, postmenopausal hormone therapy, and total energy intake in a multivariate model.

† Referent.

‡ CI, confidence interval.

§ Because of a limited distribution of intakes, the lowest two quintiles (first and second) and the next two quintiles (third and fourth) in this food group were combined.

¶ Because of a limited distribution of intakes, the middle three quintiles (second, third, and fourth) in this food group were combined.

colorectal cancer risk (69). Moreover, persons with a higher intake of fried foods tend to have a less healthy lifestyle, such as being physically inactive and overweight (70–72). Although we comprehensively controlled for lifestyle risk factors in the multivariate model, we still cannot exclude the possibility that the observed positive association might have been partly due to confounding by these and other unknown factors related to fried food intake.

The association between intake of n-3 polyunsaturated fat and colorectal cancer risk has been examined in recent years,

but results have been far from conclusive. Our study and four other studies (27, 29, 73, 74) found no clear association. However, several other studies observed an inverse association between consumption of n-3 polyunsaturated fat and colorectal cancer risk (19, 22, 30, 47, 75, 76). Interestingly, those studies with significant findings tended to be conducted in countries where consumption of fish products is not only high but also occurs over a long duration. Given that consumption of fish products in our cohort was relatively low, it is possible that intakes of n-3 polyunsaturated

fat from fish products may have been too low to exert a protective effect on colorectal cancer risk in our population.

One strength of our study is its prospective nature, which enabled us to avoid the selection and recall biases associated with case-control studies. We also had information on a wide range of potential risk factors for colorectal cancer, which allowed us to control for these variables in the analyses. However, our study also had limitations. First, estimates of nutrient intake from dietary self-reporting are subject to measurement error (e.g., underreporting of overall intake), which may result in attenuation of risk estimates (77, 78). In addition, since we only assessed food and nutrient intake once at baseline, measurement error due to random within-person variation may be inevitable. We also had limited statistical power for conducting stratified analyses because of the limited number of cases in our data. Finally, since so many nutrients were tested in the present study, our findings may be subject to chance.

In summary, our data provide little evidence that dietary fat is associated with risk of colorectal cancer. Intakes of various types of fat and major fatty acids also do not appear to be associated with risk of colorectal cancer. However, intake of fried foods and/or other factors associated with the intake may be related to cancer development. This finding warrants further examination in additional studies.

ACKNOWLEDGMENTS

This work was supported by US Public Health Service grants CA-47988 from the National Cancer Institute and HL-43851 from the National Heart, Lung, and Blood Institute.

The authors acknowledge the contributions of the staff of the Women's Health Study under the leadership of David Gordon, as well as Mary Breen, Susan Burt, Marilyn Chown, Georgina Friedenber, Inge Judge, Jean Mac-Fadyean, Geneva McNair, David Potter, Claire Ridge, and Harriet Samuelson. The authors also thank the Endpoints Committee of the Women's Health Study (Dr. Wendy Y. Chen), Lynda Rose, and Natalya Gomelskaya for technical assistance.

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