RELATION OF MEAT, FAT, AND FIBER INTAKE TO THE RISK OF COLON CANCER IN A PROSPECTIVE STUDY AMONG WOMEN

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Abstract *Background.* The rates of colon cancer in various countries are strongly correlated with the per capita consumption of red meat and animal fat and, to a lesser degree, inversely associated with the consumption of fiber.

Methods. We conducted a prospective study among 88,751 women 34 to 59 years old and without a history of cancer, inflammatory bowel disease, or familial polyposis who completed a dietary questionnaire in 1980. By 1986, during 512,488 person-years of follow-up, 150 incident cases of colon cancer had been documented.

Results. After adjustment for total energy intake, animal fat was positively associated with the risk of colon cancer (P for trend = 0.01); the relative risk for the highest as compared with the lowest quintile was 1.89 (95 percent confidence interval, 1.13 to 3.15). No association was found for vegetable fat. The relative risk of colon cancer in women who ate beef, pork, or lamb as a main dish every day was 2.49 (95 percent confidence interval, 1.24 to 5.03), as compared with those reporting consumption less than once a month. Processed meats and liver were also significantly associated with increased risk, whereas fish and chicken without skin were related to decreased risk. The ratio of the intake of red meat to the intake of chicken and fish was particularly strongly associated with an increased incidence of colon cancer (P for trend = 0.0005); the relative risk for women in the highest quintile of this ratio as compared with those in the lowest quintile was 2.49 (95 percent confidence interval, 1.50 to 4.13). A low intake of fiber from fruits appeared to contribute to the risk of colon cancer, but this relation was not statistically independent of meat intake.

Conclusions. These prospective data provide evidence for the hypothesis that a high intake of animal fat increases the risk of colon cancer, and they support existing recommendations to substitute fish and chicken for meats high in fat. (N Engl J Med 1990; 323:1664-72.)

NUTRITIONAL factors are strongly suspected of being important in causing colon cancer. In Western countries the rates of the disease are up to 10 times those of many Far Eastern and developing nations.[1] Rapid increases in rates of colon cancer among migrants from low-risk to high-risk areas[2,3] and in Japan since World War II[4,5] indicate that the large international differences are due to environmental rather than genetic causes. Although a genetic component is well established,[6] Doll and Peto[1] have suggested that differences in diet may account for 90 percent of the variation in rates among countries, but the specific factors that are responsible have not been established. Two general dietary hypotheses have evolved in recent decades[7,8]: that dietary fat, particularly from animal sources, increases the risk of colon cancer and that the intake of fiber reduces the risk.

The hypothesis that diets high in fat cause colon cancer derives largely from the striking correlations — as high as 0.89 — between the per capita consumption of meat or animal fat (but not vegetable fat) and national rates of the disease.[9,10] The recalled past diets of persons with and without colon cancer have been compared in numerous case–control investigations. Among the studies with sufficiently detailed data to calculate total fat intake, a significant positive association was found in most[11-18] but not all.[19-21] The interpretation of many studies is complicated by the frequent finding of a positive association between total energy intake and the risk of colon cancer,[11-15,18,22] raising the question of whether the total amount of food consumed or the fat composition of the diet is etiologically important. Prospective data are limited.[23-25]

Substantial data from animal and metabolic studies support a role of dietary fat in colon carcinogenesis. A high intake of saturated[26,27] and unsaturated[27,28] fat has increased the incidence of chemically induced colon cancer in animals, although not consistently.[29] In humans[30,31] and laboratory animals,[31,32] diets high in fat increase the excretion of bile acids. Increased fecal concentrations of bile acids have been found in populations with higher rates of colon cancer,[31,33] individual patients with colon cancer,[34,35] and patients with colon polyps,[36] although these findings are not entirely consistent.[37] In animal models, bile acids act as tumor promoters,[38,39] possibly by increasing the turnover of intestinal mucosal cells.[40] The tumor-enhancing effects of bile acids are increased after enzymatic modification by intestinal bacteria.[41] Colonic flora with an increased enzymatic capacity for transforming bile acids into potential carcinogens have been found in populations with high rates of colon cancer and in omnivores as compared with vegetarians[31,42]; reducing the intake of beef fat has decreased the activity of these enzymes in humans.[42,43]

Interest in the relation between the intake of fiber and colon cancer derives primarily from Burkitt's observation of low rates of colon cancer in areas of Africa where the fiber consumption and stool bulk were high.[44] Countries with a low intake of cereals tend to have high rates of colon cancer,[45,46] but the correlation is not as strong as that between fat intake and cancer rates. Inverse associations between overall fi-

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ber intake and the risk of colon cancer have been seen in some case–control studies[13,14,17,21,47-49] but not in others.[11,12,15,19,20] In several of the more recent studies, the intake of fiber from various sources was specifically examined.[12,19,49] Fiber from fruits or vegetables, but not from cereals, has been consistently associated with a lower risk of colon cancer.[5]

We examine here the intake of fat and fiber in relation to the incidence of colon cancer during six years of follow-up in a large cohort of U.S. women.[50]

Methods

The Nurses' Health Study Cohort

In 1976, 121,700 female registered nurses 30 to 55 years of age who were living in 11 large U.S. states completed a mailed questionnaire on known and suspected risk factors for cancer[51] and coronary heart disease.[52] Every two years, follow-up questionnaires have been sent to update information on potential risk factors and identify newly diagnosed cases of cancer and other diseases. In 1980, the questionnaire was expanded to include an assessment of diet.

The Semiquantitative Food-Frequency Questionnaire

A detailed description of this dietary questionnaire and documentation of its reproducibility and validity have been published elsewhere.[53-56] Briefly, we identified 61 foods that allowed maximal discrimination among the intakes of total, saturated, and monounsaturated fats, linoleic acid (the most abundant polyunsaturated fat), cholesterol, crude and total dietary fiber, and 12 other nutrients. For each food, a commonly used unit or portion size (e.g., one egg or one slice of bread) was specified, and the women were asked how often on average over the previous year they had consumed that amount of each food. There were nine possible responses, ranging from "never" to "six or more times per day." We also inquired about the types of fat used for frying and baking and at the table. The intake of nutrients was computed by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions. Composition values for dietary lipids and crude fiber were obtained from U.S. Department of Agriculture sources,[57] and the values for total dietary fiber were based on the work of Southgate and colleagues.[58,59] We adjusted nutrient values for total energy intake, using regression analysis.[22,56] Energy-adjusted values, which reflect the composition of the diet independent of the total amount of food consumed, are particularly relevant to dietary recommendations because a person's long-term intake of energy cannot change substantially without changes in physical activity or weight. In addition, controlling for total energy intake is conceptually analogous to the isocaloric conditions of feeding experiments conducted to evaluate the effects of specific nutrients.

Validation of the Dietary Questionnaire

After the 1980 dietary questionnaires were returned, we randomly selected 194 members of the cohort from the greater Boston area for a validation substudy of the instrument.[53] Each woman weighed and recorded everything she ate or drank during four one-week periods over the subsequent year. At the end of either the third or fourth week of recording, a second dietary questionnaire identical to the first was completed; 173 participants provided complete information. We used the dietary-record data to estimate the variation in the intake of nutrients in the study population and the capacity of the questionnaire to discriminate among persons according to their intake of each nutrient. Findings on the intake of lipids have been described previously[50,53]: mean intakes in the lowest and highest quintiles defined by the dietary record were 32 and 44 percent, respectively, of energy for total fat, 11 and 17 percent of energy for saturated fat, 4.2 and 8.2 percent of energy for linoleic acid, and 136 and 276 mg per 4180 kJ (1000 kcal) for cholesterol. The mean intakes of crude fiber in the lowest and highest quintiles were 1.3 and 3.2 g per 4180 kJ; data on total dietary fiber were not available from the dietary records.

Population Analysis

After up to four mailings, 98,464 women returned the 1980 dietary questionnaire. We excluded women with 10 or more food items left blank, implausibly high or low scores for total food intake, or previous cancer other than nonmelanoma skin cancer; 89,538 women remained. To avoid possible bias, these exclusions were made before the present analysis was begun. For this analysis, women with a history of ulcerative colitis or a familial polyposis syndrome were also excluded, because these conditions could affect eating behavior as well as greatly increase the risk of colon cancer. The final 1980 base-line population was thus 88,751.

Identification of Cases of Colon Cancer

Follow-up questionnaires were mailed in 1982, 1984, and 1986 to all study participants; on these forms we asked whether cancer of the colon or rectum had been diagnosed during the previous two years. Up to five mailings were sent to women who did not respond, and in 1982 and 1986 we attempted to interview the remaining women by telephone. The total rates of response were 97 percent in 1982, 90 percent in 1984, and 93 percent in 1986; the overall follow-up for nonfatal outcomes was 96 percent of the possible number of person-years.

Most deaths in the cohort are reported by family members or the postal system in response to follow-up questionnaires. In addition, we use the computerized National Death Index, a highly sensitive method of identifying deaths in this cohort,[60] to search vital records for the names of nonrespondents. Less than 1 percent of the base-line population died during the six years of follow-up.

When a case of cancer of the colon or rectum was identified from the questionnaire or vital records, we asked the participant (or next of kin, if the participant had died) for permission to obtain hospital records and pathology reports. The small number of cancers that were not adenocarcinomas were excluded, as were carcinomas in situ. In this analysis we included the 150 reported cases of invasive adenocarcinoma of the colon that were confirmed by pathology report (90 percent), by death certificate only (3 percent), or by additional written or verbal communication with the participant (7 percent). Most cancers were advanced lesions at the time of diagnosis (83 percent of the women with them have either died of their disease or had Dukes Class B or C disease at diagnosis). Only two of the Class A cancers were detected by routine screening. We excluded rectal cancer (39 cases) from the primary analysis because its epidemiologic appearance is different: in international comparisons, the rates of this cancer vary less[61] and are less clearly associated with dietary variables[9] than the rates of colon cancer.

Statistical Analysis

Women were categorized according to quintiles of intake of calories, total and specific types of fat, and other nutrients, as computed from the 1980 questionnaire. In addition, the women were classified according to their responses for individual food items. For most foods, it was necessary to collapse adjacent categories of responses in the original questions to provide a sufficient number in a group; all such combining of categories was performed before this analysis was undertaken. Body-mass index (the weight divided by the square of the height) was used as a measure of obesity.

For each participant without a diagnosis of colon cancer, follow-up time — equal to the number of months between the return of the 1980 dietary questionnaire and the 1982 questionnaire — was allocated to each dietary variable according to the status in 1980. Similarly, for the 1982-to-1984 interval and the 1984-to-1986 interval, additional person-months were allocated, again according to the 1980 dietary status. For subjects given a diagnosis of any cancer, inflammatory bowel disease, or familial polyposis and for those who died, follow-up time was allocated only up to the date of the event.

Table 1. Age-Adjusted Relative Risk of Colon Cancer According to Quintile of Total Energy Intake and Dietary Fats.*

VARIABLE	QUINTILE					χ FOR TREND (P VALUE)
	1	2	3	4	5	
Total energy (kcal/day)	<1130	1130–1389	1390–1639	1640–1959	≥1960	
Cases	31	29	34	27	29	
Person-years	99,866	103,287	105,223	101,000	103,112	
Relative risk (95% CI)	1.0	0.92 (0.56–1.53)	1.07 (0.66–1.73)	0.90 (0.54–1.50)	0.94 (0.57–1.56)	−0.26 (0.80)
Total fat (g/day)	<58	58–66	67–73	74–81	≥82	
Cases	17	38	28	38	29	
Person-years	101,841	102,292	102,283	102,972	103,100	
Relative risk (95% CI)	1.0	2.48 (1.42–4.31)	1.88 (1.03–3.44)	2.61 (1.48–4.59)	2.00 (1.10–3.63)	+1.93 (0.05)
Animal fat (g/day)	<39	39–47	48–55	56–64	≥65	
Cases	24	29	28	31	38	
Person-years	102,555	111,038	106,034	96,754	96,109	
Relative risk (95% CI)	1.0	1.22 (0.71–2.09)	1.27 (0.73–2.19)	1.55 (0.91–2.64)	1.89 (1.13–3.15)	+2.59 (0.01)
Vegetable fat (g/day)	<10	10–13	14–17	18–23	≥24	
Cases	37	29	25	33	26	
Person-years	117,939	97,287	94,325	105,171	97,768	
Relative risk (95% CI)	1.0	1.04 (0.64–1.69)	0.94 (0.56–1.56)	1.13 (0.71–1.81)	0.92 (0.55–1.53)	−0.06 (0.95)
Saturated fat (g/day)	<23	23–25	26–28	29–32	≥33	
Cases	30	22	28	41	29	
Person-years	121,912	88,420	98,661	106,664	96,832	
Relative risk (95% CI)	1.0	1.09 (0.62–1.91)	1.28 (0.76–2.15)	1.81 (1.13–2.90)	1.39 (0.83–2.33)	+1.96 (0.05)
Monounsaturated fat (g/day)	<23	23–26	27–29	30–33	≥34	
Cases	24	36	22	37	31	
Person-years	114,038	110,039	90,620	99,064	98,729	
Relative risk (95% CI)	1.0	1.74 (1.05–2.89)	1.31 (0.73–2.35)	2.03 (1.22–3.39)	1.72 (1.01–2.93)	+2.08 (0.04)
Linoleic acid (g/day)	<5.3	5.3–6.5	6.6–7.8	7.9–9.5	≥9.6	
Cases	35	32	26	32	25	
Person-years	103,435	103,246	105,032	100,262	100,514	+0.01 (0.99)
Relative risk (95% CI)	1.0	1.03 (0.64–1.66)	0.86 (0.52–1.43)	1.13 (0.69–1.85)	0.93 (0.55–1.58)	
Cholesterol (g/day)	<247	247–299	300–344	345–406	≥407	
Cases	29	31	21	30	39	
Person-years	102,586	103,625	101,776	102,704	101,798	+1.14 (0.25)
Relative risk (95% CI)	1.0	1.09 (0.66–1.82)	0.75 (0.43–1.32)	1.07 (0.64–1.77)	1.39 (0.86–2.24)	

*Adjusted for total energy intake by regression analysis to 1600 kcal per day. To convert kilocalories to kilojoules, multiply by 4184. CI denotes confidence interval.

Thus, the base-line population for any two-year interval was always alive and free of cancer and these other disorders.

Person-time for each exposure was accumulated, and an incidence rate was calculated by dividing the number of events by the person-time of follow-up. The relative risk — the incidence rate in a particular category of exposure divided by the corresponding rate in the comparison category — was used as a measure of association. Age-adjusted rates were calculated with use of five-year categories. The Mantel extension test[62] was used to evaluate linear trends across categories of dietary variables stratified according to age. Analyses to control for age and other variables simultaneously were conducted with proportional-hazards models. For all relative risks, we calculated 95 percent confidence intervals.[63]

RESULTS

During 512,488 person-years of follow-up over a six-year period, 150 cases of colon cancer were documented in the women in this cohort. Total energy intake was not significantly associated with the incidence of colon cancer (Table 1), and body-mass index was also unrelated to risk (data not shown). For energy-adjusted total intake of fat, a nonlinear relation was seen; relative risks for women in each of the four upper quintiles were significantly elevated, about twofold higher than the risk for women in the lowest quintile. When total intake of fat was divided into its primary sources, there was a significant positive trend for animal fat after adjustment for total energy intake; the relative risk for women in the highest as compared with the lowest quintile was 1.89 (95 percent confidence interval, 1.13 to 3.15; P for trend = 0.01). Positive associations were observed for both saturated fat and monounsaturated fat, the two primary constituents of animal fat. Animal fat from dairy sources was not related to the risk of colon cancer (P for trend = 0.35; relative risk = 0.91 [95 percent confidence interval, 0.55 to 1.51] for ≥18 g per day vs. <7 g per day). There was no apparent association for vegetable fat or linoleic acid, the most abundant polyunsaturated fat. Positive trends were seen for total, animal, monounsaturated, and saturated fats when the values were not adjusted for total energy intake, but these trends were weak and not statistically significant.* Despite the positive association between the risk of colon cancer and intake of animal fat, the relation between intake of animal protein and the risk of cancer was slightly inverse and not significant.

Energy-adjusted intakes of crude and total dietary fiber were both inversely associated with the risk of colon cancer, but these trends were not statistically significant (Table 2). Since previous work has suggested that fiber from various food sources may be differ-

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Table 2. Age-Adjusted Relative Risk of Colon Cancer According to Quintile of Total Dietary and Crude Fiber, and Dietary Fiber from Fruits, Vegetables, and Cereals.*

Variable	Quintile					χ for Trend (P Value)
	1	2	3	4	5	
Total dietary fiber (g/day)	<11.6	11.6–14.3	14.4–17.2	17.3–21.2	≥21.3	
Cases	30	23	38	24	35	
Person-years	102,902	102,449	102,833	104,150	100,154	
Relative risk (95% CI)	1.0	0.74 (0.43–1.28)	1.16 (0.72–1.88)	0.69 (0.40–1.17)	0.90 (0.54–1.49)	−0.38 (0.70)
Total crude fiber (g/day)	<2.7	2.7–3.3	3.4–4.0	4.1–5.0	≥5.1	
Cases	29	25	35	33	28	
Person-years	104,272	104,742	103,719	105,433	94,323	
Relative risk (95% CI)	1.0	0.81 (0.47–1.37)	1.06 (0.65–1.74)	0.87 (0.52–1.45)	0.71 (0.41–1.23)	−0.77 (0.44)
Fruit fiber† (g/day)	<0.8	0.8–1.6	1.7–2.6	2.7–4.0	≥4.1	
Cases	31	30	30	31	28	
Person-years	103,811	102,195	103,075	102,026	101,381	
Relative risk (95% CI)	1.0	0.94 (0.57–1.55)	0.87 (0.53–1.44)	0.81 (0.49–1.34)	0.62 (0.37–1.05)	−1.56 (0.12)
Vegetable fiber‡ (g/day)	<3.8	3.8–5.1	5.2–6.8	6.9–9.3	≥9.4	
Cases	29	30	31	24	36	
Person-years	102,258	101,939	102,073	101,985	104,233	
Relative risk (95% CI)	1.0	1.02 (0.61–1.71)	1.03 (0.62–1.72)	0.78 (0.43–1.34)	1.07 (0.65–1.76)	−0.17 (0.87)
Cereal fiber§ (g/day)	<2.8	2.8–3.9	4.0–5.2	5.3–7.0	≥7.1	
Cases	34	25	21	39	31	
Person-years	102,722	102,611	102,436	102,132	102,587	
Relative risk (95% CI)	1.0	0.72 (0.43–1.21)	0.58 (0.34–1.00)	1.04 (0.65–1.64)	0.74 (0.43–1.21)	−0.49 (0.62)

*Adjusted for total energy intake by regression analysis to 1600 kcal per day. To convert kilocalories to kilojoules, multiply by 4184. CI denotes confidence interval.

†Includes crude fiber from fresh apples or pears; oranges; orange or grapefruit juice; peaches, apricots, or plums; and other fruits.

‡Includes crude fiber from string beans; broccoli; cabbage, cauliflower, or brussels sprouts; carrots; corn; spinach or other greens; peas or lima beans; yellow squash; sweet potatoes; beans or lentils; and tomatoes or tomato juice.

§Includes crude fiber from rice or pasta, cold breakfast cereal, white bread, dark or whole-grain bread, cake, and cookies.

entially related to colon cancer, we computed the contributions of crude fiber from fruits, vegetables, cereals, and other sources. When examined in relation to the risk of colon cancer, only fiber from fruit was associated with any appreciable reduction in risk, and the overall trend did not attain statistical significance. For women in the highest quintile of the energy-adjusted intake of fruit fiber as compared with those in the lowest quintile, the relative risk of colon cancer was 0.62 (95 percent confidence interval, 0.37 to 1.05).

Because dietary factors are unlikely to influence directly the incidence of colon cancers diagnosed early in the follow-up period, we repeated our analyses after excluding cases diagnosed between the 1980 and 1982 questionnaires. For the 103 cases that occurred during the most recent four years of follow-up, the association with the intake of animal fat was stronger (relative risk for highest vs. lowest quintiles, 2.52; 95 percent confidence interval, 1.34 to 4.76; P for trend = 0.002). The association with the intakes of crude and total dietary fiber did not change appreciably.

Women who consumed diets high in animal fat tended to consume less fiber (Spearman correlations for energy-adjusted values, −0.40 for crude fiber and −0.38 for total dietary fiber). We therefore examined the risk of colon cancer among women simultaneously classified according to their intakes of both animal fat and crude fiber. For women in the highest category of animal-fat intake and the lowest quintile of energy-adjusted crude-fiber intake (as compared with those in the lowest and highest quintiles, respectively), the risk of colon cancer was further increased (relative risk, 2.52; 95 percent confidence interval, 1.00 to 6.34).

We also examined specific foods in relation to risk of colon cancer (Table 3). Of the 61 foods included in the questionnaire, the strongest association was with beef, pork, or lamb eaten as a main dish; women who reported daily consumption had 2½ times the risk of those who reported eating such meals less than once a month (P for trend = 0.01). Positive trends were also seen with the consumption of processed meats (P for trend = 0.04) and liver (P for trend = 0.03). On the other hand, women who reported eating chicken without skin two or more times a week had half the risk of colon cancer of women who ate it less than once a month (P for trend = 0.03). Fewer women reported eating chicken with skin, which was not associated with the risk of colon cancer (P for trend = 0.65). An inverse trend was seen with fish consumption, although this did not attain statistical significance (P = 0.09). Whole milk, cheese, and ice cream, which are other sources of animal fat, were not significantly related to the risk of colon cancer; indeed, no other food on the questionnaire approached a significant positive or inverse association (P for trend <0.10). Although no single food accounted for the inverse relation of fruit fiber to the risk of colon cancer, inverse trends were seen for apples or pears (P = 0.16), oranges (P = 0.16), and bananas (P = 0.13).*

The association of specific foods with the risk of colon cancer may be difficult to interpret because of intercorrelations; for example, fish and chicken are often recommended as substitutes for red meats, and their intakes were thus inversely correlated (r = −0.21). To represent this pattern of substitution, we computed the total intake of red meats (the consump-

Table 3. Age-Adjusted Relative Risks for Foods Associated with the Incidence of Colon Cancer.*

Food	Frequency						χ for Trend (P Value)
	<1/mo	1–3/mo	1/wk	2–4/wk	5–6/wk	≥1/day	
Beef, pork, or lamb as a main dish							
Cases	14	42		57	18	16	
Person-years	65,345	156,488		208,897	50,494	30,240	
Relative risk (95% CI)	1.0	1.39 (0.75–2.56)		1.50 (0.84–2.70)	1.84 (0.90–3.75)	2.49 (1.24–5.03)	+2.52 (0.01)
Processed meats							
Cases	46	36	32	28	7		
Person-years	160,464	139,127	104,072	78,528	27,311		
Relative risk (95% CI)	1.0	1.09 (0.70–1.69)	1.45 (0.91–2.31)	1.86 (1.16–2.98)	1.21 (0.53–2.72)		+2.07 (0.04)
Chicken without skin							
Cases	37	25	57	19			
Person-years	120,472	74,836	168,859	100,187			
Relative risk (95% CI)	1.0	1.00 (0.60–1.66)	0.96 (0.63–1.45)	0.47 (0.27–0.82)			−2.15 (0.03)
Fish							
Cases	12	59	54	19	5		
Person-years	43,948	173,019	200,732	77,277	15,356		
Relative risk (95% CI)	1.0	1.29 (0.70–2.40)	0.92 (0.49–1.72)	0.75 (0.35–1.58)	1.06 (0.36–3.12)		−1.67 (0.09)
	Never	≤1/mo	2–3/mo	≥1/wk			
Liver†							
Cases	39	73	27	10			
Person-years	167,452	266,543	61,742	15,951			
Relative risk (95% CI)	1.0	1.00 (0.68–1.49)	1.51 (0.93–2.47)	2.01 (1.01–4.02)			+2.16 (0.03)

*Values add to less than the total number of subjects because of missing responses for specific foods. CI denotes confidence interval.

†The question on liver was asked in a slightly different format because of the relatively low frequency of consumption.

tion of beef, pork, and lamb from all sources), the total intake of chicken and fish, and the ratio of these totals (Table 4). As expected from the findings for individual foods, total consumption of red meat was positively associated with the risk of colon cancer, and total intake of chicken and fish was related to a reduced incidence of the disease. When the women were divided into quintiles according to the ratio of red meat to chicken and fish in their diets, those in the highest quintile were approximately 2½ times more likely to have colon cancer than those in the lowest quintile (relative risk, 2.49 [95 percent confidence interval, 1.50 to 4.13]; P for trend = 0.0005). A similar association was seen when the total intakes of red meat and chicken plus fish were expressed as a difference rather than a ratio, to reflect absolute consumption (relative risk for highest vs. lowest quintile, 2.44; 95 percent confidence interval, 1.44 to 4.14). The strong association between the ratio of red meat to chicken plus fish and the risk of colon cancer could not be clearly attributed to only one of these inversely correlated variables; when the variables (each adjusted for total

Table 4. Age-Adjusted Relative Risk of Colon Cancer According to Quintile of Consumption of Red Meat, Consumption of Chicken and Fish, and the Ratio between Them.*

Variable	Quintile					χ for Trend (P Value)
	1	2	3	4	5	
Red meat† (g/day)	<59	59–83	84–105	106–133	≥134	
Cases	25	27	28	26	44	
Person-years	97,680	100,565	100,299	100,402	111,879	
Relative risk (95% CI)	1.0	1.16 (0.67–1.99)	1.25 (0.73–2.13)	1.13 (0.65–1.97)	1.77 (1.09–2.88)	+2.20 (0.03)
Chicken and fish‡ (g/day)	<22	22–28	29–40	41–64	≥65	
Cases	38	29	39	19	25	
Person-years	99,641	102,400	103,950	102,489	102,345	
Relative risk (95% CI)	1.0	0.75 (0.46–1.22)	0.99 (0.63–1.54)	0.47 (0.27–0.81)	0.56 (0.34–0.92)	−2.63 (0.009)
Ratio of red meat to chicken and fish	<1.2	1.2–2.0	2.1–3.2	3.3–5.1	≥5.2	
Cases	22	26	27	29	46	
Person-years	101,091	100,999	103,016	101,965	103,754	
Relative risk (95% CI)	1.0	1.33 (0.75–2.37)	1.43 (0.80–2.54)	1.60 (0.90–2.83)	2.49 (1.50–4.13)	+3.47 (0.0005)

*The analyses excluded 292 women who ate no red meat, chicken, or fish, because the ratio would have been undefined. CI denotes confidence interval.

†Red meat included beef, pork, or lamb as a main dish (steak, roast, or ham, for example); beef, pork, or lamb as a sandwich or mixed dish (stew, casserole, or lasagna, for example); hamburger; hot dogs; preserved meats (sausage, salami, or bologna, for example); and bacon. The intake of red meat was adjusted for total energy intake by regression analysis to 6700 kJ (1600 kcal) per day.

‡Chicken and fish include chicken with skin, chicken without skin, and fish. The intake was adjusted for total energy intake by regression analysis to 6700 kJ (1600 kcal) per day.

energy intake) were entered simultaneously in a proportional-hazards model that also included total energy intake, the relative risks were 0.63 (95 percent confidence interval, 0.39 to 1.00) for the highest quintile of chicken-plus-fish intake and 1.61 (95 percent confidence interval, 1.03 to 2.53) for the highest quintile of red-meat intake. The relation of this ratio to the incidence of colon cancer changed little and remained significant when entered in multivariate models that included total energy intake and the intake of one of the following: calcium, vitamin D, vitamin C, vitamin E, carotene, total vitamin A, total dietary fiber, crude fiber, or fruit fiber. Moreover, none of these other variables were significant when included in these models.

Although the focus of the present analysis was on cancer of the colon, we also examined relations separately for the 39 cases of rectal cancer and for the combination of colon and rectal cancers. No clear associations were seen with this small number of cases of rectal cancer, except for a trend of increasing risk with a higher ratio of red meat to chicken plus fish in the diet (P for trend = 0.08). For colon and rectal cancers combined, the association with the intake of animal fat was thus weaker than for colon cancer alone (relative risk for highest vs. lowest quintile, 1.64 [95 percent confidence interval, 1.04 to 2.57]; P for trend = 0.03), and the association with the ratio of red meat to chicken plus fish was similar (relative risk, 2.30 [95 percent confidence interval, 1.48 to 3.56]; P for trend <0.0001).

Discussion

These prospective data provide evidence for the hypothesis that a higher consumption of red meat and fat from animal sources increases the incidence of colon cancer independently of total energy intake. Previous studies of diet and colon cancer in individual persons have provided inconsistent support for this hypothesis, which is derived largely from international correlations. Total intake of fat was associated with a higher risk of colon or rectal cancer in most[11-18] but not all[19-21] case–control studies. In only two[17,64] was the fat composition of the diet shown to be significantly related to risk independently of total energy intake. The intake of meat has been associated with the risk of colon cancer in other case–control studies,[65-69] but not in a study from Japan.[70]

The few prospective studies of diet and colon cancer have been seriously limited by the methods used to assess diet or the small number of incident cases. On the basis of a single 24-hour recall and approximately 20 years of follow-up, an inverse association between the intake of saturated fats and the risk of colon cancer was found among Japanese-Hawaiian men[23]; no association was found between the intake of fat and 49 deaths due to colon or rectal cancer among Chicago men during a similar period of follow-up.[24] Colon cancer was positively associated with the intake of processed meat in Norway[71] and inversely related to meat intake in Japan[72]; however, the amounts of meat in the diet were probably small in the Japanese study conducted in the early 1960s. Although Seventh-Day Adventists consume less meat than the general U.S. population and have only about half the risk of colon cancer,[73] the intake of meat (including poultry) was not associated with the risk of the disease in one prospective study in this religious group.[74] However, even the heaviest meat eaters among the Seventh-Day Adventists ate relatively small amounts as compared with the women in our study. In a preliminary report on another cohort of 35,000 Adventists, those in the highest third according to intake of animal fat had a significantly increased risk of colon cancer (relative risk as compared with the lowest third, 1.80).[25] Although quantitative data were not provided, meat (beef and lamb) was noted to be the only food associated with the risk of colon cancer in a 14-year follow-up of 16,477 Swedish men and women.[75]

Whether the composition of fat ingested influences the risk of colon cancer has important implications. In our study and a Canadian case–control study,[11] the positive association with dietary fat was limited to saturated and monounsaturated fats; the intake of linoleic acid was not related to the risk of colon cancer. In two European studies,[19,21] the consumption of vegetable fat was inversely related to the incidence of colon cancer. The differences in the fat composition of beef (ratio of polyunsaturated to saturated fatty acid, 0.1), chicken (ratio, 0.7), and fish (high in n−3 fatty acids)[57] may relate to the contrasting associations of these foods with the incidence of colon cancer in our data. Because in most studies vegetable fat was consumed in lower quantities than animal fat, we cannot exclude the possibility that vegetable fat would increase the risk of colon cancer if it were consumed in much greater amounts.

The association of red meat with the risk of colon

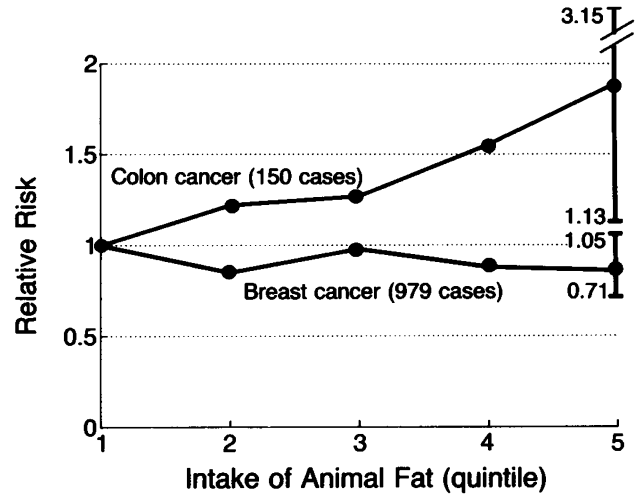

Figure 1. Relative Risks of Colon and Breast Cancer According to Intake of Animal Fat, Adjusted for Total Energy Intake, during Six Years of Follow-up.

The bars represent 95 percent confidence intervals for the women in the highest quintile.

cancer may be due to its fat content. However, other hypotheses suggest that Western diets high in meat augment rates of colon cancer by increasing the fecal concentration of endogenous nitrosamines,[76] carcinogenic tryptophan metabolites,[77] or carcinogens resulting from the cooking of meat.[78] In this study, however, the percentage of time that meat was eaten well done was unrelated to the risk of colon cancer (data not shown). Some processed meats and bacon may contain nitrosamines that could add to the risk of colon cancer beyond the fat contributed by these foods. Although we cannot be certain that the association between the risk of cancer and the intake of red meat is due to fat content, this association can still provide practical guidance for making dietary decisions.

The present study provides some suggestion that a high intake of fruits containing fiber may contribute to a lower risk of colon cancer. Although the inverse associations with foods containing fiber were not statistically significant, a clearer relation might emerge with continued follow-up. In the present analysis, the chief food sources of vitamin C (orange juice) and β-carotene (carrots) were not appreciably associated with risk of colon cancer.

Biased recall of diet was eliminated in this study because all data on food intake were collected before the diagnosis of colon cancer. However, nondietary risk factors for colon cancer, such as sedentary lifestyle,[17,75,79,80] could have produced our findings if strongly associated with the intake of animal fat and red meat. However, controlling for physical activity (assessed in 1980 as the usual time spent in vigorous or moderate activity on weekdays and weekend days) did not alter the association of the intake of animal fat or meat with the risk of colon cancer in this study. We did not collect data on family history of colon cancer until 1982. Among women without colon cancer in 1982, however, we found no material differences in fat or fiber intake between women with a paternal, maternal, or sibling history of colon cancer and women of a similar age who had no such history. Uncontrolled confounding by total energy intake cannot explain our findings, because total energy intake was only slightly and nonsignificantly related to the risk of colon cancer and, in the validation substudy, total energy intake as measured by dietary record was not correlated with the energy-adjusted intake of animal fat as measured by our questionnaire ($r = 0.05$).

Our findings are most directly generalizable to nonvegetarian U.S. women; only 290 women in this cohort (0.3 percent) did not regularly eat red meat, fish, or poultry. The substitution of other protein sources, such as beans or lentils, for red meat might also be associated with a reduced risk of colon cancer in populations that consume more legumes. Whether our findings also apply to colon cancer in men must be addressed by prospective studies among men. Given, however, that similar associations have been found for men and women between rates of colon cancer and the intake of animal fat internationally[9] and between the intake of saturated fat and monounsaturated fat in the case–control studies with findings most similar to ours,[11,17] the relations in our study are likely to be similar in men.

The absence of a positive association between dietary fat and breast cancer in this same cohort[50] has been questioned because of possibly inadequate variation in fat intake in the study population and imperfect measurement of fat intake.[81,82] The present analysis indicates that the variation in fat intake in this population and its measurement are sufficient to detect important associations with disease. With six years of follow-up, confidence intervals do not overlap for breast and colon cancer among women in the highest quintile of animal-fat intake (Fig. 1). Thus, the association between the intake of animal fat and the risk of colon cancer and the absence of a positive association between dietary fat and the incidence of breast cancer in this cohort add to evidence[5] that breast and colon cancers have different relations to fat intake.

Our findings provide evidence for the hypothesis that the intake of fat, primarily of animal origin, increases the risk of colon cancer, but they are also compatible with the possibility that other factors in red meat raise the incidence of the disease. Most directly, these data lend support to existing dietary recommendations[83,84] to reduce one's intake of meats high in fat and to substitute fish and chicken.

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REVIEW ARTICLE

DRUG THERAPY

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HISTAMINE$_2$-RECEPTOR ANTAGONISTS

Standard Therapy for Acid-Peptic Diseases

(First of Two Parts)

MARK FELDMAN, M.D.,
AND MICHAEL E. BURTON, PHARM.D.

THIS article reviews the clinical pharmacology of histamine$_2$-receptor antagonist drugs (H_2 blockers) and their usefulness in the treatment and prevention of acid-peptic disorders — namely, peptic ulcer disease, Zollinger–Ellison syndrome, gastroesophageal reflux disease, and acute stress ulcers and erosions. Erosive gastritis and erosive duodenitis are often considered acid-peptic diseases, but because they overlap with peptic ulcer disease they are not considered as separate entities in this review. Non-ulcer dyspepsia is not included as an acid-peptic disorder since it does not appear to respond to therapy with H_2 blockers or antacids.[1] H_2 blockers are quite effective in some acid-peptic disorders, whereas their effectiveness in others is less apparent. For such conditions, newer agents such as sucralfate, misoprostol, and omeprazole may prove to have advantages over H_2 blockers, but H_2 blockers are the standard therapy against which newer agents will be compared for efficacy and safety.

CLINICAL PHARMACOLOGY OF H_2 BLOCKERS

The chemical structures of the four H_2 blockers currently marketed in the United States — cimetidine, ranitidine, famotidine, and nizatidine — are shown in Figure 1.

Gastric Actions

The histamine receptors on the basolateral membrane of the acid-secreting parietal cell are of the H_2 type and thus are not blocked by conventional H_1 antihistamines such as diphenhydramine.[2] The occupation of H_2 receptors by histamine, released from mast cells and possibly other cells, activates adenylate cyclase, increasing intracellular concentrations of cyclic AMP. The increased levels of cyclic AMP activate the proton pump of the parietal cell, a hydrogen, potassium-ATPase, to secrete hydrogen ions against a large concentration gradient in exchange for potassium ions (Fig. 2). H_2 blockers competitively and selectively inhibit the binding of histamine to H_2 receptors, thereby reducing both intracellular concentrations of cyclic AMP and the secretion of acid by the parietal cells. These cells also contain receptors for gastrins (primarily G_{17} and G_{34}) and receptors for acetylcholine (muscarinic type), both of which activate the cells by increasing intracellular calcium.[2] There appears to be an in vivo interaction between the cyclic AMP pathway (activated by histamine) and the calcium pathway activated by gastrin or acetylcholine or both, and perhaps also by histamine.[3]

The relative potencies of the four H_2 blockers in inhibiting the secretion of gastric acid vary from 20- to 50-fold; cimetidine is the least potent and famotidine the most potent (Table 1).[4-12] The effective concentrations required for inhibition of 50 percent of the pentagastrin-stimulated secretion of gastric acid in humans in vivo are also shown in Table 1. With ordinary doses, the duration of a serum concentration above the level for 50 percent inhibition ranges from approximately 6 hours for cimetidine to approximately 10 hours for nizatidine, ranitidine, and famotidine.[4-10]

As a result of inhibiting the secretion of gastric acid and raising gastric pH, all H_2 blockers tend to increase fasting serum concentrations of gastrin by an average of 10 to 20 ng per liter and concentrations after eating by 30 to 40 ng per liter.[13] Peptic activity is reduced by all four drugs because of a decrease in the secretion of pepsinogen and the fact that as gastric pH rises above 4, pepsin is much less active.[14] None of the four agents have produced any consistent effect on lower esophageal sphincter function or gastric emptying.[15-26]

After therapy with H_2 blockers is discontinued,

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