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Diet and colon cancer in Los Angeles County, California

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The diets of 746 colon cancer cases in Los Angeles County, California (USA) were compared with those of 746 controls matched on age, sex, race, and neighborhood. In both genders, total energy intake was associated with significantly increased risk, and calcium intake was associated with significantly decreased risk. These effects were reduced only slightly after adjustment for the nondietary risk factors (weight, physical activity, family history, and, if female, pregnancy history). In men, total fat and alcohol intakes were responsible for the calorie effect; in women, no individual source of calories was associated independently with risk. Neither saturated fat nor fat from animal sources was responsible for the fat effect. There were no additional independent significant effects for sucrose, fiber, cruciferous vegetables, β-carotene, other vitamins, or any other nutrient or micronutrient. In univariate analyses, meats, poultry, breads, and sweets were associated with excess risk, and yogurt was protective. After adjustment for sources of calories, no individual food was associated with excess risk, but yogurt remained significantly protective. Total calories were associated with excess risk throughout the colon while the effects of calcium, fat, and alcohol appeared somewhat stronger in the distal colon. After adjustment, crude fiber was significantly protective in the ascending colon but not even weakly protective in the distal colon.

Key words: Alcohol, calcium, calories, coffee, colon cancer, cruciferous vegetables, diet, fat, fiber, protein, United States, vitamins.

Introduction

Diet is believed to play an important role in the etiology of colon cancer, and the Western diet especially has been implicated since migrants from countries with low rates of this tumor generally assume the higher rates of Western countries within one or two generations.[1] The specific aspects of diet that may alter risk, however, have not been established. A broad range of dietary factors have been implicated: with increased risks often (but not always) linked to heavy consumption of meat, fat (especially saturated fat), protein, and alcohol; and decreased risks associated with increased intakes of fruits, vegetables (especially cruciferous vegetables), fiber-containing foods, and dairy products.

We examined dietary factors in a population-based case-control study of colon cancer involving 746 matched pairs. Using a semi-quantitative food-frequency questionnaire and food models to illustrate portion sizes, we attempted to obtain a diet history sufficiently complete to examine specific components of the total diet.

Materials and methods

Subject selection

Cases were English-speaking White men and women

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with invasive histologically confirmed adenocarcinoma of the colon who were first diagnosed between November 1983 and June 1986, and identified by the Cancer Surveillance Program, the tumor registry covering all residents of Los Angeles County, California (United States).[2] Eligibility was limited to cases who were between 45 and 69 years of age at diagnosis and born in the US, Canada, or Western Europe. Cases were excluded if no primary subsite could be identified from the pathology report ($n = 9$), or if there was a family history of *polyposis coli* ($n = 1$), or a personal history of inflammatory bowel disease ($n = 8$). Cases also were excluded if the histologic subtype was carcinoid ($n = 9$), or if the primary site was the appendix ($n = 3$), since there is evidence to suggest these may have a distinct etiology.[3,4]

Altogether, 1,066 eligible cases were identified. The patient's hospital or physician refused to grant permission to contact 86 of these cases; 76 had died or were too sick to be interviewed; and 29 had moved from the area or could not be located. Of the remaining 875 patients, 106 declined to be interviewed. Interviews were completed with 769 cases, representing 72 percent of those originally identified and 88 percent of those approached.

One White English-speaking control born in the US, Canada, or Europe was matched individually to each case on sex, date of birth (within five years), and neighborhood. We excluded as controls subjects with a family history of *polyposis coli* or a personal history of inflammatory bowel disease. Controls were identified by an algorithm that used the house of the index case as a reference point and proceeded in a systematic and invariable sequence until a maximum of 200 residential units had been canvassed. Efforts were made to interview, as the control, the first eligible resident in this sequence; no control was interviewed until it was established that there was no willing match earlier in the sequence. Letters were left when no-one was home, and follow-up by mail, telephone, and site visits continued until either an eligible control agreed to be interviewed or 200 housing units had been screened. If the first eligible match refused to participate, the second eligible match in the sequence was asked to participate and so on. Willing eligible controls were located for all but 23 of the interviewed cases. The 746 interviewed controls were found after screening an average of 25.1 housing units; no match resided in 95 percent of the intervening units; no census could be completed in four percent, and eligible but unwilling persons resided in the remaining two percent. The first eligible match was interviewed for 475 (63.7 percent) of the cases; the second eligible match was interviewed for 169 (22.7 percent) of the remaining cases.

Interview/questionnaire

Both case and matching control were interviewed in person by the same interviewer, usually in the home of the respondent. It was not possible to blind the interviewers to the case or control status of the subjects, but study hypotheses were not discussed with the interviewers. The same structured questionnaire was used for all interviews; it was designed primarily to assess diet over the previous 15 years, and physical activity and weight changes during the previous 30 years. All four interviewers were trained by the first author and the same Master's level dietitian who herself was one of the interviewers. The interviewers met weekly during the first six months and biweekly thereafter to review their interviews, with the goal of making sure they were handling all probes and special circumstances the same way.

Diet was assessed with a modified version of the semi-quantitative food-frequency questionnaire (SFFQ) developed and validated by Willett and his colleagues.[5-7] In its original form, the SFFQ consists of a four-page printed Diet Assessment which asks respondents how often they usually consume a specified portion of 116 foods and drinks, with nine response categories ranging from less than once a month to six or more times a day. Additional items in the SFFQ not presented in the frequency format include:

- the kinds of fat (*i.e.*, butter, lard, margarine, vegetable shortening, or vegetable oil) usually used for frying and baking:
- the form of margarine (*i.e.*, stick, tub, diet) usually used:
- the proportion of the visible fat on meats generally eaten:
- the amounts of bran and sugar added to food:
- usual brands of cold breakfast cereal; and
- use of vitamin supplements.

Rather than having subjects fill out this diet assessment on their own, our interviewers asked each question during the interview and filled out the printed form, which was sent to Willett for machine-scoring and analysis. Subjects were asked to recall their diets during a specified reference year, usually two years before the diagnosis year of the case for both case and matched control, but always a year considered by the subject to be representative of his or her diet over the previous 15 years. A 30-year life-events calendar, which was filled out immediately before the diet portion of the interview, was used to help subjects pinpoint any important changes in their diets. Generic food models placed on or in standard plates, bowls, glasses, and spoons were used to illustrate portion sizes, and adjustments were made in the frequency of

consumption if subjects typically ate or drank larger or smaller portions than those described on the questionnaire. In addition to the foods listed on the original SFFQ, subjects were asked about 23 additional foods which previous food surveys among residents of Los Angeles County identified as important local sources of major nutrients (*e.g.*, avocado, papaya, and coconut). When any of these foods were consumed at least weekly, they were added to the open-ended section on additional foods.

The Diet Assessments were checked for completeness and stray pencil marks before they were mailed to Willett, and subjects were re-contacted when there were questions or omissions. Open-ended items were coded by registered dietitians in Boston before the forms were machine-scored.

Analysis

Measures of total calories, total fat, and fat components were adjusted for reported trimming of visible fat from meats. Vitamin and mineral intakes were examined both with and without reported use of dietary supplements, with no substantive differences in risk estimates. Results reported here include only the intake from foods.

The pathology reports were examined to confirm the histologic diagnosis of invasive adenocarcinoma and identify the primary subsite of each tumor. All analyses were performed with the complete set of pairs and separately within sex, subsite, and sex-subsite groups. Divisions for the subsite analyses were made between the ascending colon and hepatic flexure, and between the descending colon and sigmoid.

Standard statistical methods for the analysis of matched case-control studies were used.[8] Results are given as relative risks (RR) per specified unit of intake, with RRs computed as the exponential of the logistic regression coefficient. The RRs were estimated by matched odds ratios except for the subsite analyses; here, all controls were pooled and compared with cases within each subsite, in a stratified analysis matching within 24 age-sex-social-class strata (ages ≤ 54, 55-59, 60-64, and 65+, for men and women and three socioeconomic strata based on income, education, and socioeconomic class of neighborhood of residence). Trends were assessed by the score test χ-square using continuous (uncategorized) nutrient variables. All reported *P*-values are two-sided.

Quintiles were based on the distribution of consumption among same-gender controls. The unit of intake for RRs was 100 calories per day for total calories and all individual sources of calories, 10 servings per month for all food items, and the average daily amount of a dietary component needed to move a subject from one quintile to the next, equally weighted by sex, for fiber, vitamins, and minerals. (Appendix A shows, for typical servings of various common foods and beverages, the approximate number of calories from fat, protein, carbohydrate, and alcohol, and the approximate number of mg of calcium.)

Multivariate logistic regression was used to adjust the dietary variables for the following nondietary risk factors that had significant, independent effects, but are not discussed in this paper: family history; weight; physical activity; and, if female, pregnancy history. The adjustment variables used were: (i) a family history index which summed the number of first- and second-degree relatives with cancer of the large bowel, giving first-degree relatives a weighting of two and coding total index values greater than three as three; (ii) self-reported weight 10 years before diagnosis; (iii) the usual hours per day spent in light or moderate physical activities five years prior to diagnosis; and (iv) for pregnancy history, both linear and quadratic forms of both the number of full-term pregnancies and the number of incomplete pregnancies.[9]

The main results of our investigation of the contributions of different sources of calories to risk are given in Table 2. This table shows the results of fitting, in separate multivariate logistic regressions, various combinations of sources of calories, calcium, and the nondietary risk factors. The various fitted combinations are referred to as 'models' for ease of reference in the text. The statistical significance of differences in the fit of two (appropriately embedded) models is computed in the standard manner, *i.e.*, taking the difference in the associated χ-square tests as a χ-square on the difference in degrees of freedom of the two models being compared.

Results

Of the 746 cases, 327 were female and 419 were male. Cases were distributed by primary subsite as follows: 118 in the cecum; 77 in the ascending colon; 30 at the hepatic flexure; 52 in the transverse colon; 37 at the splenic flexure; 68 in the descending colon; and 364 in the sigmoid. There was a greater tendency among males for the tumors to cluster at the distal end of the colon (53 percent of tumors in males were in the sigmoid compared with 44 percent in females), while females had proportionally more tumors in the cecum and ascending colon (31 percent *cf* 22 percent for females and males, respectively). Of all tumors located in the sigmoid, mid-colon, and cecum/ascending colon respectively, 60 percent, 56 percent, and 48 percent were in males.

Because of the matching procedure, controls were similar to cases in their distributions by age, education, and income. The average age of all subjects was 61.4 (± 6.0). Males and females had an average of 13.5 (± 3.0) and 12.8 (± 2.4) years of education, respectively. As expected, average daily intake of total calories and all major macronutrients were greater among males than females (Table 1). The same was true for most micronutrients, except that females had greater intakes of vitamin A and β-carotene.

Total calories

Overall, cases consumed significantly more calories than controls (2,472.2 *cf* 2,302.8, matched $P = 0.0002$). Risk of colon cancer increased monotonically with successive quintiles of calorie consumption. The RRs for quintiles 2 through 5 compared with the first quintile were: 1.30 (95 per cent confidence interval [CI] = 0.92-1.84); 1.37 (CI = 0.98-1.92); 1.46 (CI = 1.04-2.04); and 1.82 (CI = 1.30-2.53). On average, risk increased by 2.3 percent per 100 calories per day (Table 2, Model 1). This univariate calorie effect was somewhat stronger in men (2.8 percent) than in women (1.6 percent) and only slightly reduced after adjustment for the nondietary risk factors (from 2.3 percent to 1.9 percent per 100 calories [Models 1 and 2]).

Calcium

All dietary components were examined both before and after adjustment for total calories. The most striking finding with this procedure was that while there was essentially no effect for calcium in a univariate analysis, after adjustment for total calories, increasing calcium intake was significantly associated with decreasing risk (RR per 295 mg calcium daily = 0.85, $P = 0.0003$) (Table 2, Model 3). This calorie-adjusted protective effect of calcium was statistically significant in both genders and of similar magnitude, both before and after adjustment for the nondietary risk factors. For all subjects together, the RRs for quintiles 2 through 5 compared with the first quintile, after adjustment for the four sources of calories and the nondietary risk factors were: 1.01 (CI = 0.71-1.44); 0.63 (CI = 0.43-0.93); 0.59 (CI = 0.40-0.89); and 0.42 (CI = 0.25-0.69).

Individual sources of calories

The tendency for cases to consume more calories than controls was not limited to any one source of calories. Cases consumed significantly more of every source of calories—fat, protein, carbohydrates (excluding alcohol), and alcohol—and significantly more of every component of fat—saturated fat, monounsaturated fat, and polyunsaturated fat (Table 1). With the exception of alcohol, each source of calories was highly correlated with each other source of calories as well as with total calories (Table 3).

When the four primary sources of calories were entered simultaneously into a multivariate logistic regression, only calories from alcohol were identified as a statistically significant, independent risk factor (Table 2, Model 4) for males and all subjects combined. Calories from fat also were a statistically significant independent risk-factor in males, but was only of borderline statistical significance when both genders were combined. There was, however, a statistically significant improvement in the overall model χ-square when calories from fat and alcohol combined as a single variable and calories from other sources (carbohydrate and protein) were substituted for total calories (Model 5 *cf* Model 3; 117.87 − 112.09 = 5.78 on one degree of freedom). This means the effects of fat and alcohol were significantly different from the effects of protein and carbohydrates. For females, total calories was a significant risk factor after calcium was included in the model (Model 3), but no individual source of calories was statistically significantly different from the other sources of calories (Model 4) since the change in the model χ-square after separating the sources of calories was trivial (55.45 − 55.10 = 0.35 on three degrees of freedom). In both sexes, of the nonalcohol sources of calories, protein appeared to contribute the largest increased risk per 100 calories (10 percent), but this effect was not statistically significant (independent of the other sources of calories).

There were no statistically significant interactions between sex and the effects of any source of calories. Even though only calories from fat and alcohol appeared to have statistically significant independent effects, all subsequent adjusted analyses reported in the body of this paper included simultaneous adjustment for all four sources of calories—since it may be argued that all micronutrients and other food components require adjustment for total energy intake even in the absence of an independent calorie effect,[10] and fat and alcohol did not account for the excess risk linked to total calories in women. Since a more traditional approach to the analysis of this type of data, however, involves adjusting each source of calories individually for total calories (as a combined variable), the results of additional models based on this traditional approach have been included in Appendix B.

Fat

When the three major types of fat (saturated, monounsaturated, and polyunsaturated) were entered simultaneously into the logistic regression as a replacement

Table 1. Average daily intakes (and standard deviations) of major macronutrients and selected micronutrients for cases and controls by sex, colon cancer, Los Angeles County

	All subjects ($n = 746$ pairs)		Males ($n = 419$ pairs)		Females ($n = 327$ pairs)	
	Cases	Controls	Cases	Controls	Cases	Controls
Calories	2,472.2 (945.3)	2,302.8[a] (818.1)	2,682.9 (995.4)	2,460.0[a] (842.5)	2,202.3 (800.9)	2,101.3[b] (739.6)
Fat (g)	98.4 (43.7)	90.9[a] (37.6)	106.6 (46.8)	96.5[a] (38.7)	87.9 (36.9)	83.7 (34.9)
Protein (g)	98.4 (36.1)	93.3[c] (30.4)	104.1 (39.1)	97.0[c] (31.8)	91.2 (30.6)	88.6 (27.9)
Carbohydrates (g) (excluding alcohol)	276.8 (117.0)	264.2[d] (107.0)	291.1 (120.0)	279.1 (109.8)	258.4 (110.4)	245.1 (100.3)
Alcohol (g)	19.4 (29.7)	14.8[c] (24.0)	27.5 (35.1)	19.5[a] (27.3)	8.9 (15.5)	8.7 (10.7)
Dietary fiber (g)	25.8 (14.1)	24.8 (11.5)	25.8 (13.1)	25.3 (12.1)	25.8 (15.2)	24.2 (10.7)
Crude fiber (g)	6.5 (2.8)	6.3 (2.6)	6.5 (2.9)	6.3 (2.6)	6.5 (2.7)	6.2 (2.6)
Saturated fat (g)	34.1 (16.9)	31.7[c] (14.5)	37.2 (18.2)	34.0[c] (15.4)	30.1 (14.3)	28.7 (12.7)
Monounsaturated fat (g)	34.7 (16.2)	32.0[a] (14.0)	37.9 (17.3)	34.2[a] (14.3)	30.7 (13.6)	29.2 (13.0)
Polyunsaturated fat (g)	19.0 (9.0)	17.7[d] (8.0)	20.3 (9.5)	18.3[c] (7.9)	17.4 (7.9)	16.8 (8.1)
Calcium (mg)	1,044.5 (543.3)	1,048.6 (503.6)	1,106.8 (574.1)	1,089.4 (540.0)	964.6 (490.5)	996.3 (448.1)
Vitamin D (IU)	319.9 (191.3)	319.7 (176.8)	340.1 (205.1)	333.7 (189.7)	294.1 (168.9)	301.7 (157.2)
Phosphate (mg)	1,645.0 (636.9)	1,590.4[b] (574.2)	1,749.4 (664.8)	1,664.7[b] (600.5)	1,511.3 (573.1)	1,495.3 (524.5)
Vitamin C (mg)	165.3 (83.3)	159.0 (83.2)	163.9 (86.4)	160.1 (86.2)	167.1 (79.3)	157.6 (79.2)
β-carotene (IU/1000)	11.3 (7.4)	11.1 (7.4)	10.6 (7.4)	10.5 (7.0)	12.1 (7.4)	11.8 (7.9)
Vitamin A (IU/1000)	14.6 (8.2)	14.4 (8.2)	14.1 (8.1)	13.8 (7.7)	15.3 (8.2)	15.1 (8.7)
Vitamin E (mg, tocopherol equivalent)	11.1 (5.7)	10.5[d] (5.0)	11.4 (6.0)	10.5[d] (4.9)	10.7 (5.4)	10.5 (5.1)
Iron (mg)	16.1 (6.4)	15.1[a] (5.5)	16.8 (6.9)	15.7[c] (5.5)	15.2 (5.6)	14.3[b] (5.5)
Zinc (mg)	16.2 (6.2)	15.1[a] (5.4)	17.1 (6.6)	15.8[c] (5.7)	15.0 (5.5)	14.3[b] (5.0)
Caffeine (mg)	357.6 (258.3)	348.2 (259.2)	366.4 (263.4)	355.6 (265.7)	346.5 (251.8)	338.6 (250.8)
Sucrose (g)	75.9 (56.9)	71.2[b] (51.5)	79.7 (57.5)	77.2 (54.6)	71.0 (55.8)	63.4[b] (46.1)

[a] $P < 0.001$.
[b] $P < 0.10$.
[c] $P < 0.01$.
[d] $P < 0.05$.

Table 2. Matched relative risks (RR)[a] and 95% confidence intervals (CI) for sources of calories (per 100 calories) and calcium (per 295 grams), by sex, colon cancer, Los Angeles county

	All subjects (n = 746 pairs)		Males (n = 419 pairs)		Females (n = 327 pairs)	
	RR[a]	(CI)	RR[a]	(CI)	RR[a]	(CI)
Model 1						
Calories	1.02	(1.01-1.04)[b]	1.03	(1.01-1.04)[b]	1.02	(1.00-1.04)
Model 1 χ-square (df)	14.17	(1)	12.40	(1)	2.62	(1)
Model 2: The nondietary risk factors[c] plus...						
Calories	1.02	(1.01-1.03)[d]	1.02	(1.01-1.04)[d]	1.01	(0.99-1.03)
Model 2 χ-square (df)	98.57	(8)	51.48	(4)	48.58	(8)
Model 3: The nondietary risk factors[c] plus...						
Calories	1.04	(1.02-1.06)[b]	1.05	(1.02-1.07)[b]	1.04	(1.01-1.07)[f]
Calcium (per 295 g)	0.85	(0.78-0.93)[b]	0.86	(0.77-0.96)[d]	0.82	(0.70-0.96)[f]
Model 3 χ-square (df)	112.09	(9)	59.05	(5)	55.10	(9)
Model 4: The nondietary risk factors[c], calcium, plus...						
Fat	1.06	(1.00-1.12)[b]	1.08	(1.00-1.17)[f]	1.01	(0.92-1.12)
Protein	1.10	(0.91-1.33)	1.10	(0.87-1.40)	1.09	(0.80-1.50)
Carbohydrate	1.00	(0.97-1.04)	0.99	(0.94-1.04)	1.05	(0.98-1.13)
Alcohol	1.10	(1.04-1.17)[d]	1.11	(1.04-1.19)[d]	1.05	(0.90-1.23)
Model 4 χ-square (df)	119.06	(12)	68.23	(8)	55.45	(12)
Model 5: The nondietary risk factors[c], calcium, plus...						
Fat + alcohol	1.09	(1.05-1.13)[b]	1.11	(1.06-1.16)[b]	1.03	(0.95-1.10)
Carbohydrate + protein	1.01	(0.97-1.04)	0.99	(0.95-1.04)	1.05	(0.99-1.12)
Model 5 χ-square (df)	117.87	(10)	67.47	(6)	55.27	(10)
Model 6: The nondietary risk factors[c], calcium, protein, carbohydrate, alcohol, plus...						
Saturated fat	1.19	(0.90-1.56)	1.05	(0.73-1.51)	1.34	(0.87-2.07)
Monounsaturated fat	0.92	(0.62-1.36)	1.03	(0.62-1.70)	0.78	(0.41-1.49)
Polyunsaturated fat	1.09	(0.77-1.54)	1.23	(0.79-1.90)	0.92	(0.51-1.66)
Model 6 χ-square (df)	119.11	(14)	68.27	(10)	58.13	(14)
Model 7: The nondietary risk factors[c], calcium, protein, carbohydrate, alcohol, plus...						
Fat from animal sources	1.07	(0.99-1.17)[e]	1.06	(0.95-1.19)	1.06	(0.92-1.23)
Fat from vegetable sources	1.04	(0.96-1.13)	1.10	(0.99-1.22)[e]	0.98	(0.86-1.11)
Model 7 χ-square (df)	119.35	(13)	68.41	(9)	56.22	(13)
Model 8: The nondietary risk factors[c], calcium, fat, protein, carbohydrate, plus...						
Alcohol from beer	1.06	(0.95-1.17)	1.08	(0.96-1.21)	0.93	(0.69-1.27)
Alcohol from liquor	1.11	(1.02-1.22)[f]	1.10	(1.00-1.22)[e]	1.10	(0.90-1.35)
Alcohol from white wine	1.35	(0.96-1.89)[e]	1.41	(0.94-2.10)[e]	1.29	(0.66-2.54)
Alcohol from red wine	0.98	(0.71-1.35)	1.07	(0.73-1.38)	0.70	(0.34-1.42)
Model 8 χ-square (df)	121.33	(15)	69.95	(11)	57.83	(15)
Model 9: The nondietary risk factors[c], calcium, fat, protein, alcohol, plus...						
Sucrose	1.00	(0.93-1.07)	0.97	(0.89-1.06)	1.07	(0.94-1.22)
Nonsucrose carbohydrates	1.01	(0.94-1.08)	1.00	(0.92-1.09)	1.04	(0.92-1.16)
Model 9 χ-square (df)	119.07	(13)	68.47	(9)	55.59	(13)

[a] Matched RRs per 100 calories (or, in the case of calcium, per 295 g), adjusted for all variables in the same model.
[b] P-value for trend < 0.001.
[c] Family history, weight, physical activity, and, if female, pregnancies (as four variables).
[d] P-value for trend < 0.01.
[e] P-value for trend < 0.10.
[f] P-value for trend < 0.05.

for total fat, none was statistically significantly different from the other two (Table 2, Model 6 *cf* Model 4); thus, no single type of fat explained the risk observed for total fat. Saturated fat was associated with the greatest risk in females and overall, but polyunsaturated fat was associated with the greatest risk in males. Similarly, when fats from animal and vegetable sources were separated and entered simultaneously into a model (replacing total fat), fat from animal sources appeared to convey somewhat greater risk overall and in women, while fat from vegetable sources was associated with greater risk in men (Table 2, Model 7). Still, the effects of these two sources of fat were statistically indistinguishable, since the improvement in the overall model χ-square was trivial.

Alcohol

The effects of alcohol were stronger and statistically significant only in males (Table 2, Model 4), but there was no statistically significant interaction between alcohol and gender. There also appeared to be no increase in risk associated with fewer than 75 alcoholic drinks per month in either gender, after which risk increasing consumption was associated wth a pattern of increasing risks in both genders (Table 4). However, the data are compatible with a single linear effect, since there was no substantive improvement in the model when a quadratic form of alcohol or a dichotomous term (75 or more drinks per month) was substituted for calories from alcohol.

When alcohol calories from beer, liquor, white wine, and red wine were separated and entered simultaneously into a logistic regression model (replacing total alcohol), there was no statistically significant improvement in the model χ-square (Model 4 *cf* Model 8). Alcohol from hard liquor was the only source of alcohol independently associated with a statistically significant increase in risk, but the largest RR was with white wine, which was marginally significant. This latter effect was influenced strongly by outliers—five cases and one control who reported drinking four or more glasses of white wine per day. Similarly, the RR associated with beer was reduced by a reversal in an otherwise overall pattern of increasing risk in the highest category of consumption (where only 15 cases but 16 controls reported drinking six or more beers daily).

Sucrose

Sucrose, which is highly correlated with total carbohydrates ($r = 0.84$), was associated with increased risk before adjustment (Table 1). This excess risk was marginally significant in females and overall. When calories from both sucrose and nonsucrose carbohydrates were entered simultaneously into the multiple logistic regression (replacing calories from carbohydrates), they were not statistically distinguishable (Table 2, Model 9 *cf* Model 4). While, in women, sucrose appeared to carry a somewhat greater risk than nonsucrose carbohydrates, the opposite was true in men and overall.

Fiber

Fiber was not associated with statistically significant effects in this study, either before (Table 2) or after (Table 5) adjustment for all sources of calories, calcium, and the nondietary risk factors. A weak, nonsignificant, protective pattern was present for adjusted

Table 3. Correlation coefficients between intakes of major sources of calories and nutrients for all subjects (n = 1,492), colon cancer, Los Angeles county

	Fat	Protein	Carbohydrate	Alcohol	Dietary fiber	Calcium	Vitamin D	Phosphate	Vitamin C	β-carotene	Vitamin E	Iron	Zinc
Calories	0.91	0.86	0.89	0.29	0.56	0.68	0.48	0.85	0.46	0.28	0.62	0.73	0.82
Fat		0.85	0.70	0.10	0.44	0.61	0.43	0.78	0.29	0.21	0.63	0.65	0.81
Protein			0.70	0.08	0.55	0.73	0.56	0.91	0.42	0.35	0.58	0.74	0.91
Carbohydrate				0.05	0.64	0.64	0.48	0.77	0.58	0.35	0.57	0.70	0.67
Alcohol					−0.04	0.02	−0.04	0.07	−0.01	−0.09	−0.01	−0.05	0.09
Dietary fiber						0.46	0.28	0.62	0.49	0.47	0.51	0.63	0.55
Calcium							0.78	0.89	0.35	0.27	0.41	0.46	0.60
Vitamin D								0.72	0.27	0.24	0.32	0.36	0.44
Phosphate									0.43	0.35	0.58	0.72	0.84
Vitamin C										0.42	0.42	0.47	0.37
β-carotene											0.36	0.37	0.30
Vitamin E												0.73	0.56
Iron													0.78

Table 4. Matched relative risks (RR)[a], 95% confidence intervals (CI), and *P*-values for trend by number of alcohol-containing drinks per month, by sex, colon cancer, Los Angeles county

Alcoholic drinks per month	All		Males			Females		
	RR[a]	(CI)	Cases/controls	RR[a]	(CI)	Cases/controls	RR[a]	(CI)
None	1.00		87/107	1.00		137/129	1.0	
1-10	0.84	(0.60-1.18)	66/83	0.95	(0.58-1.57)	65/78	0.78	(0.49-1.25)
11-29	1.02	(0.71-1.46)	60/63	1.14	(0.68-1.89)	51/52	0.93	(0.56-1.55)
30-74	0.90	(0.61-1.33)	59/68	0.98	(0.57-1.66)	36/34	0.84	(0.46-1.55)
75-99	1.28	(0.83-1.98)	48/36	1.46	(0.84-2.55)	21/20	1.04	(0.49-2.20)
100+	1.67	(1.13-2.47)	99/62	1.84	(1.15-2.96)	17/14	1.42	(0.61-3.32)
Trend	$P = 0.009$		$P = 0.005$			$P > 0.50$		

[a] Adjusted for fat, protein, carbohydrates, calcium, and the nondietary risk factors (family history, activity level, weight, and, if female, pregnancies).

Table 5. Matched relative risks (RR)[a] per unit[b] and 95% confidence intervals (CI) for fiber and selected vitamins, minerals, and other dietary components, by sex, colon cancer, Los Angeles county

Nutrient	Unit[b]	All subjects ($n = 746$ pairs)		Males ($n = 419$ pairs)		Females ($n = 327$ pairs)	
		RR[a]	(CI)	RR[a]	(CI)	RR[a]	(CI)
Dietary fiber	7 g	1.01	(0.93-1.09)	0.97	(0.86-1.09)	1.06	(0.93-1.20)
Crude fiber	2 g	1.00	(0.88-1.14)	0.98	(0.84-1.16)	1.03	(0.82-1.29)
Vitamin D	108 IU	1.08	(0.97-1.20)	1.10	(0.95-1.26)	1.08	(0.90-1.28)
Phosphate	335 mg	1.07	(0.79-1.44)	1.09	(0.74-1.58)	1.07	(0.65-1.77)
β-carotene	3,700 IU	0.99	(0.93-1.05)	0.98	(0.90-1.07)	0.99	(0.90-1.09)
Vitamin A	4,350 IU	0.98	(0.91-1.05)	0.97	(0.88-1.07)	0.99	(0.89-1.10)
Vitamin C	45 mg	1.02	(0.94-1.10)	0.99	(0.90-1.09)	1.05	(0.92-1.20)
Vitamin E	3 mg	0.99	(0.91-1.08)	1.02	(0.91-1.14)	0.96	(0.84-1.09)
Iron	3 mg	1.08	(0.98-1.18)	1.06	(0.93-1.20)	1.11	(0.95-1.28)
Zinc	3 mg	1.04	(0.90-1.20)	1.02	(0.85-1.23)	1.09	(0.86-1.37)
Caffeine	183 mg	0.98	(0.91-1.07)	0.95	(0.86-1.06)	1.02	(0.90-1.17)

[a] Adjusted for fat, protein, carbohydrates, alcohol, calcium, and the nondietary risk factors (family history, weight, physical activity, and, if female, pregnancies).

[b] Unit = average amount of nutrient needed to move a subject from one quintile to the next, equally weighted by sex.

fiber intake in males, but not in females or overall. No consistent pattern of risk emerged from an examination of fiber by fiber type (dietary or crude [Table 5]) or source (fruits, vegetables, grains, or all other [data not shown]).

Vitamins A, C, D, and E

There were very weak, nonsignificant protective effects from adjusted intakes of β-carotene and vitamin A in both men and women (Table 5). Vitamin C was weakly protective in men but not women while the reverse was true for vitamin E. Vitamin D intake is highly correlated with calcium intake (Table 3); when calcium was omitted from the adjusted models, a protective pattern for vitamin D emerged in both men and women but did not reach statistical significance, even when both genders were combined. When calcium was included in the adjusted model, there was no evidence of any residual protective pattern for vitamin D (Table 5).

Protein, iron, and zinc

Before any adjustments, protein intake was significantly positively associated with risk, especially in men (Table 1). When all sources of calories were entered in the model simultaneously, the magnitude of the effect for protein remained strong, but it was no longer statistically significant (Table 2). Protein intake is highly correlated with intakes of iron and zinc (Table 3); both of these micronutrients had statistically significant, positive, univariate associations with colon cancer in

both men and women (Table 1). After adjustment for protein and the other risk factors, some positive residual effects of iron and zinc appeared to persist, especially for iron, but were no longer statistically significant (Table 5).

Phosphate

Phosphate, which is highly correlated with protein, calcium, and zinc (Table 3), was associated with borderline significantly increased risk in univariate analysis (RR for 335 mg phosphate = 1.05, $P = 0.08$), a strikingly significant increased risk when adjusted only for calcium (comparable RR = 1.33, $P < 0.0001$) (data not shown), and minimal nonsignificant residual risk when adjusted for all sources of calories as well as calcium and the nondietary risk factors (RR = 1.07, $P > 0.50$) (Table 5). The source of calories primarily responsible for the reduction in risk from 1.33 to 1.07 in the latter model is protein (RR for 335 mg of phosphate after adjustment only for calcium and protein = 1.10, $P = 0.45$).

Caffeine

Before adjustment for calories and the other risk factors, caffeine was associated with slight nonsignificant increased risk in both men and women. After adjustment, however, a weak, nonsignificant, protective pattern emerged in men and overall (Table 5).

Specific foods

Before adjustment, consumption of red meats, processed meats, and poultry was associated with statistically significant increased risks of colon cancer (Table 6). For the most part, these increased risks were roughly equal in men and women, unchanged after adjustment only for the nondietary risk factors, and no longer statistically significant after additional adjustment for sources of calories. Consumption of seafood increased risk only in women but this was not statistically significant either in women or overall (Table 6).

Consumption of yogurt was protective in both men and women. This protective trend remained statistically significant after adjustment for calcium, sources of calories, and the nondietary risk factors (Table 6). There was also a weak protective pattern for consumption of milk, which was of borderline significance in females before adjustment. After adjustment, milk was no longer protective as long as calcium was in the model (Table 6). When calcium was omitted from the model, however, consumption of milk was protective in both genders (RR per 10 servings per month = 0.97, CI = 0.94-0.99).

There were virtually no effects associated with fruits or vegetables, including cruciferous vegetables, either before or after adjustment. Potatoes were associated with a marginally significant increased risk before adjustment, no risk after adjustment for the nondietary risk factors, and weak (nonsignificant) protection after additional adjustment for sources of calories. Breads, sweets, and sweet beverages were associated with increased risk univariately in both genders, which was not altered by adjustment for the nondietary risk factors. However, most of this excess risk was lost after adjustment for sources of calories. Breakfast cereals were associated with decreased risk in males but significantly increased risk in females before adjustment; after adjustment for calories, cereals were no longer linked to risk in either gender.

Decaffeinated coffee was associated with a weak protective effect with marginal statistical significance in men but not women. Regular coffee was not linked to risk in either direction. Adjustment did not alter the effects for either type of coffee.

Subsite analyses

The excess risk associated with total calories was present throughout the colon (Table 7). The protective effect of calcium, however, was stronger in the distal colon, and this was true for both men and women. In general, it appeared that the effects of fat, protein, and nutrients highly correlated with these factors (iron, zinc, and phosphate) also had their strongest effects in the sigmoid colon. The effect of iron was marginally significant in the sigmoid even after adjustment. The adjusted effect of alcohol was strongest in the mid-colon, but in men, the alcohol effect was equally strong in the sigmoid.

The adjusted effects of fiber were protective only in the ascending colon; this protective effect was statistically significant for crude but not dietary fiber (Table 7). The adjusted effects of virtually all the vitamins and minerals were also weakly (but nonsignificantly) protective in the proximal but not distal colon. In contrast, the adjusted effect of caffeine was weakly (but nonsignificantly) protective in the sigmoid but not in the more proximal segments of the colon.

Discussion

In this study, both total energy intake and calcium were identified as significant independent contributors to risk of colon cancer in both men and women. These

Table 6. Matched relative risks (RR) (per 10 servings per month) and 95% confidence intervals (CI) for selected foods and food groups for all subjects combined

Nutrient	Unit in servings per month	Males	Females	All subjects		All subjects	
		Crude RR per unit	Crude RR per unit	Crude RR per unit	(CI)	Adjusted[a] RR per unit	(CI)
Red meat (beef, pork, or lamb, as sandwich, mixed dish, or main dish)	10	1.18[b]	1.14[c]	1.16	(1.09-1.26)[d]	1.04	(0.92-1.19)
Processed meats (bacon, hot dogs, sausage, salami, bologna, etc.)	10	1.05	1.12[e]	1.06	(1.01-1.12)[c]	0.99	(0.93-1.06)
Poultry (chicken and turkey)	10	1.23[e]	1.21	1.22	(1.02-1.47)[c]	1.18	(0.94-1.48)
Seafood (fresh fish, canned fish, and shellfish)	10	1.02	1.19	1.09	(0.93-1.27)	1.00	(0.83-1.21)
Milk (whole, low-fat, and skim)	10	1.00	0.95[e]	0.98	(0.96-1.01)	1.04	(0.98-1.10)
Yogurt	10	0.80[e]	0.83[e]	0.82	(0.71-0.94)[b]	0.83	(0.70-0.98)[c]
Fruits (fresh, frozen, or canned)	10	1.00	1.02	1.01	(0.99-1.03)	1.00	(0.97-1.03)
Cruciferous vegetables (broccoli, cabbage, cauliflower, etc.)	10	1.00	1.00	1.00	(0.99-1.01)	1.00	(0.99-1.01)
Potatoes (baked, boiled, mashed, and fried)	10	1.08	1.13	1.10	(1.00-1.21)[e]	0.98	(0.87-1.10)
Other noncruciferous vegetables	10	1.02	1.03	1.03	(1.00-1.05)	1.01	(0.97-1.04)
Breads (including sweet rolls and doughnuts)	10	1.04[b]	1.04[e]	1.04	(1.02-1.06)[d]	1.02	(0.99-1.07)
Breakfast cereals (hot and cold)	10	0.96	1.17[c]	1.03	(0.95-1.13)	1.01	(0.89-1.16)
Pasta, rice, and whole grains	10	1.03	0.87	0.97	(0.84-1.12)	0.87	(0.73-1.03)
Peanut butter, nuts and other legumes	10	1.07[c]	0.95	1.02	(0.97-1.06)	0.98	(0.93-1.03)
Candy, ice cream, cookies, and other sweets and desserts	10	1.01	1.03	1.02	(1.00-1.04)[e]	1.01	(0.97-1.04)
Sweet beverages (juices, and sweetened soft drinks)	10	1.03	1.04	1.04	(1.00-1.07)[c]	1.02	(0.98-1.07)
Coffee (regular)	10	1.01	0.99	1.00	(0.99-1.02)	1.00	(0.98-1.01)
Decaffeinated coffee	10	0.97[e]	1.02	0.99	(0.96-1.01)	0.98	(0.95-1.01)

[a] Adjusted for fat, protein, carbohydrates, alcohol, calcium, and the nondietary risk factors (family history, weight, physical activity, and, if female, pregnancy history).
[b] P-value for trend < 0.01.
[c] P-value for trend < 0.05.
[d] P-value for trend < 0.001.
[e] P-value for trend < 0.10.

Table 7. Relative risks (RR)[a] per unit[b] and 95% confidence intervals (CI) for total calories and selected nutrients by subsite for all subjects combined

Nutrient	Unit[b]	Ascending colon (195 cases/746 controls)		Transverse and descending colon (187 cases/746 controls)		Sigmoid colon (364 cases/746 controls)	
		RR[a] per Unit	(CI)	RR[a] per Unit	(CI)	RR[a] per Unit	(CI)
Calories	100 cal	1.04	(1.01-1.06)[c]	1.03	(1.00-1.06)[d]	1.05	(1.03-1.07)[e]
Calcium	295 mg	0.91	(0.78-1.05)	0.87	(0.74-1.01)[f]	0.86	(0.77-0.97)[d]
Fat	100 cal	1.04	(0.95-1.14)	1.07	(0.97-1.18)	1.08	(1.00-1.16)[d]
Protein	100 cal	1.07	(0.80-1.42)	0.89	(0.66-1.18)	1.16	(0.93-1.45)
Carbohydrate	100 cal	1.02	(0.96-1.08)	1.02	(0.96-1.09)	0.99	(0.95-1.04)
Alcohol	100 cal	1.06	(0.97-1.17)	1.12	(1.03-1.23)[d]	1.08	(1.01-1.16)[d]
Dietary fiber	7 g	0.97	(0.85-1.11)	1.05	(0.91-1.21)	1.01	(0.90-1.13)
Crude fiber	2 g	0.80	(0.65-0.99)[d]	1.04	(0.85-1.28)	1.08	(0.93-1.26)
β-carotene	3,700 IU	0.96	(0.87-1.06)	0.95	(0.86-1.06)	1.04	(0.97-1.11)
Vitamin A	4,350 IU	0.95	(0.85-1.05)	0.94	(0.83-1.06)	1.04	(0.96-1.13)
Vitamin C	45 mg	0.99	(0.89-1.12)	1.00	(0.88-1.12)	1.05	(0.95-1.15)
Vitamin D	108 IU	0.97	(0.83-1.15)	1.08	(0.91-1.29)	1.11	(0.98-1.26)
Vitamin E	3 mg	0.95	(0.82-1.09)	0.99	(0.87-1.13)	1.03	(0.94-1.14)
Iron	3 mg	0.99	(0.86-1.14)	0.96	(0.83-1.12)	1.10	(0.99-1.23)[f]
Zinc	3 mg	0.87	(0.70-1.09)	1.02	(0.83-1.25)	1.08	(0.91-1.28)
Phosphate	335 mg	0.70	(0.45-1.10)	0.98	(0.63-1.55)	1.29	(0.91-1.83)
Caffeine	183 mg	1.01	(0.90-1.15)	1.00	(0.88-1.13)	0.98	(0.89-1.07)

[a] All RRs are based on all controls in a stratified analysis matched with 24 age-sex-social class strata, and adjusted for fat, protein, carbohydrates, alcohol, calcium, and the nondietary risk factors (family history, weight, physical activity, and, if female, pregnancies).
Note: Calories are adjusted only for calcium and the nondietary risk factors.

[b] Unit = either 100 calories of macronutrient or average amount of food component needed to move a subject from one quintile to the next, equally weighted by sex.

[c] P-value for trend < 0.01.

[d] P-value for trend < 0.05.

[e] P-value for trend < 0.001.

[f] P-value for trend < 0.10.

two aspects of diet, however, had opposite effects, and were negatively confounded, each masking the effects of the other when considered univariately. In men, the sources of calories primarily responsible for the increased risk linked to total energy intake were total fat and alcohol. In women, no individual source of calories could be identified as responsible. Saturated fat and fat from animal sources were not more important predictors of risk than polyunsaturated fat and fat from vegetable sources.

This study has a number of strengths. First, it is one of the largest case-control studies of diet and colon cancer conducted to date. Second, the dietary findings reported here are adjusted not only for each other and all other sources of calories, but also for all nondietary factors known to be associated with risk in these subjects, including body size and physical activity. Third, the semi-quantitative food-frequency questionnaire used to assess past dietary intake, which has been validated in previous studies,[6,7] is especially good at capturing a wide variety of calorie sources (*e.g.*, 13 categories of sweets and baked goods; 17 categories of breads, cereals, and starches; and 18 categories of juices and other beverages) that are sometimes overlooked when such questionnaires are used. Fourth, the SFFQ was enhanced not only by the addition of 23 foods known to be commonly consumed in the Los Angeles area but also the use of in-person interviews, food models to demonstrate portion sizes, and a life-events calendar to help subjects focus on the period of interest. Finally, we believe the quality of the data is high since the same interviewer always interviewed both case and matching control, a single data control clerk checked the coding of all questionnaires throughout the study, and the interviewers made a conscious effort to follow the same uniform script and use the same probes for the same circumstances; not only did they meet regularly to share their handling of special circumstances but they also periodically observed each other's interviews in the field throughout the study.

Despite these strengths, all case-control studies of diet and cancer have limitations that also must be con-

sidered. First, compared with interviewed cases, patients who died, were too ill to be interviewed, or who refused to participate may have consumed fewer calories, more calcium, more saturated fat or less fiber, leading to an explanation of our findings on the basis of selection bias. This seems unlikely since interviewed cases did not differ from eligible cases who were not interviewed on characteristics on which we had information, *i.e.*, marital status, social class, religion, subsite, and duration of symptoms. Further, a similar case-control study in which the next of kin was interviewed for a sample of deceased patients did not find differences in the dietary patterns between these patients and those included in their study.[11]

Second, eligible controls who were willing to be interviewed may have been more health-conscious than eligible but unwilling controls, thereby consuming fewer calories and more calcium than the true non-diseased population. While this is a possibility, it seems unlikely because these same controls did not consume more fiber, more vitamins, and much less saturated fat than cases; and these are the dietary components upon which health-conscious persons most frequently focus. Also, the distributions of dietary components in this study for controls are similar to those reported in other studies using this[12] and similar methods[13] of assessing diet.

Finally, the possibility of recall bias cannot be totally ruled out. Cases may have made efforts to change their diets after their diagnoses and thereby inadvertently exaggerated the quantities they had consumed during the previous 15 years. Again, however, if this were true, one would expect them to exaggerate their consumption of saturated over nonsaturated fats and reduce their recalled intakes of fiber and various vitamins; apparently they did not.

In general, our univariate findings of increasing risks linked to increasing intakes of total calories, total fat, and meats are consistent with the findings of most epidemiologic studies of colon cancer that have examined these aspects of diet.[14,15] Like the mixed findings in many of the published studies, however, our findings for these three highly intercorrelated variables are not totally consistent across gender, with the most important effect appearing to be for total fat in men and total calories in women, even though the magnitude of the effects for total calories and meat were roughly similar for both men and women. We did not find saturated fat to be the primary source of the excess risk associated with fat. In males, where the fat effect was strongest, the risk associated with polyunsaturated fats was actually higher than that linked to saturated fats, even though statistically these were not distinguishable from each other. On the other hand, it is interesting that in women, where there was no statistically significant univariate effect for either total calories or calories from fat, saturated fat was the only source of fat for which risk was elevated in the adjusted model.

All consumed calories are either stored (resulting in weight gain), expended, or expelled. Energy is expended through four mechanisms: physical activity; resting metabolic rate; the thermogenic effect of food (*i.e.*, energy expended to absorb and process food); and adaptive thermogenesis (*i.e.*, the capacity to conserve or expend energy in response to temperature extremes or variable intake of food).[16] Since the average weight-difference between cases and controls in this study is only 2.7 kg, the higher calorie intake but lower physical activity of cases compared with controls appears to be contradictory.[10] If, in fact, cases consumed more calories than controls, even after allowing for weight and physical activity, then it would seem that cases either digest food less efficiently or have a higher expenditure of energy through their basal metabolic rates or thermogenesis. It is also possible that the apparent effect of calories observed in this study is due to recall bias, with cases simply overreporting consumption of food. Since we have no measures of digestive efficiency, basal metabolic rate, or thermogenesis, we have no way of knowing whether recall bias or real differences in the handling of food explains the observed effect of calorie consumption. One therefore should be cautious in interpreting this calorie effect in women, where no single source of calories was shown to differ in its effect. In men, where it is clear that calories from fat and alcohol have different effects than calories from protein and carbohydrate, generalized recall bias would not affect our conclusions.

The hypothesis that calcium plays a protective role in colon carcinogenesis is not new, and has been the subject of a number of recent reviews.[17-20] Generally speaking, animal studies have produced more consistent support for this hypothesis than human or epidemiologic studies. Thus, the fact that the protective effects of calcium reported here were strong negatively confounded with the excess risk linked to total energy intake is potentially important. This means that total energy intake and calcium are capable of masking the effects of each other, and could explain why studies that examine their effects only separately may observe neither. In the univariate analyses for this study, there was a statistically significant effect for total energy intake only in men and no significant effect for calcium in either gender. Only when total calories and calcium were in the same model were their effects both statistically significant and of roughly the same magnitude in both genders. One other case-control study, also conducted in a US population, reported similar (but

weaker) negative confounding between these same two aspects of diet, but in that study, the univariate effects of both total energy and calcium were statistically significant as well.[21]

Men consumed at least twice as much alcohol as women in this study, and hard liquor was the source of 47 percent of this alcohol intake among the men and 53 percent among the women. Thus, it should not be surprising that only alcohol from hard liquor was statistically significant, even though the different sources of alcohol were not highly correlated (correlation coefficients ranged from − 0.01 between white wine and beer to + 0.18 between red wine and liquor) and their effects were statistically indistinguishable from each other. A similar effect for consumption of 'spirits' was observed in both sexes by Potter and his colleagues in South Australia, but there the finding was stronger in women than in men.[22] We are aware of only one other case-control study in which alcohol consumption was linked significantly to colon (as opposed to rectal) cancer; in that study, the effect was present only in males.[23] A number of other case-control studies conducted in Canada, Australia, and Great Britain reported positive but nonsignificant associations with alcohol,[24-26] but several recent studies from mainland Europe found either a protective effect[27] or no effect at all.[28,29] Cohort studies, on the other hand, usually have reported statistically significant, positive associations between alcohol intake and future colon cancer.[30-33]

While not all epidemiologic studies of diet and colon cancer report protective effects for intakes of fiber, vegetables, and/or vitamins associated with fruits and vegetables, the majority have observed such a pattern. These studies have been reviewed recently[34-35] and subjected to meta-analyses;[35] intakes of fiber and vegetables were found to be generally protective. In the current study, both male and female cases reported consuming more fiber and more vegetables than controls, just as they reported consuming more of every major source of calories and most foods. After adjustment only for the four sources of calories, there was a weak nonsignificant protective effect for both dietary and crude fiber, β-carotene, and vitamin C; these effects were invariably stronger in males. However, after adjustment for calcium and the nondietary risk factors as well as for sources of energy, even these weak protective effects were diminished. Nonetheless, weak protective effects for these dietary components persisted for the ascending colon, even after adjustment, and intake of crude (but not dietary) fiber was statistically significant for this subsite. Most investigators tend to emphasize dietary rather than crude fiber, but at least one previous study observed stronger and more consistent effects for crude than dietary fiber.[36] This same study, however, observed these effects about equally in the upper and lower colon. Another case-control study whose findings were reported by subsite within the colon found stronger and more consistent protective effects for (dietary) fiber for left- than for right-sided tumors.[27]

The protective effect observed in this study for consumption of yogurt was not expected. This effect was present in both sexes and independent of the other risk factors including the protective effect for calcium. Yogurt consumption could be a marker for some other unmeasured healthy behavior, expecially since consuming yogurt as infrequently as one to three times a month conferred almost as much protection as more frequent consumption. Alternatively, there could be something in yogurt (besides calcium) that protects the colon from cancer. The latency or induction time for experimental colon cancer has been shown to be increased in rats fed *Lactobacillus acidophilus*, the most common bacteria added to milk to make yogurt.[37] In humans, supplements of *Lactobacillus acidophilus* have been shown to decrease fecal bacterial β-glucuronidase and nitroreductase activities, which returned to baseline levels 30 days after the *Lactobacillus* supplements were stopped.[38] A protective effect for 'cultured milk' was also observed in a small population-based case-control study conducted recently in Wisconsin.[39] In that study, the protective effect associated with consuming cultured milk was strongest and of borderline significance for diets consumed after age 35, weaker but still present for diets between ages 18 and 35, and essentially nonexistent for diets consumed before age 18.

Frequent coffee consumption has been linked both to increased[23,40] and decreased[41-45] risks of colon cancer. Those studies that observed the increased risks were conducted in populations at low risk of colon cancer, Seventh-day Adventists[40] and Mormons;[23] but the protective effects of coffee were observed in a wide range of populations from all over the world, including the low risk populations of Singapore[44] and Japan.[43] In this study involving a generally high-risk population, there were virtually no risks, either increased or decreased, associated with caffeine, regular coffee, or decaffeinated coffee.

Our findings do not support the hypothesis that sweets and starchy foods devoid of fiber are linked to greater risk of colon cancer than other carbohydrates or sources of calories.[46] Similarly, we found no support for a protective effect of dietary vitamin D that is independent of calcium,[17-47] or an increased risk linked to phosphate that is independent of protein and other sources of calories.[48]

It is apparent that most dietary determinants of

colon cancer are highly intercorrelated and that at least some are capable of masking the effects of others. It is important that future epidemiologic studies of diet and colon cancer obtain complete estimates of total energy intake as well as other potential sources of confounding. Examination of the effects of different dietary components simultaneously in multivariate models is a useful method of teasing out the relative importance of these factors.

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Appendix A

Table A1. Approximate calories of fat, protein, carbohydrate, and alcohol, and mg of calcium in selected common foods

	Approximate calories				Calcium (mg)
	Fat	Protein	Carbohydrate	Alcohol	
5 oz of beef[a]	405	130	0	0	15
5 oz of chicken (no skin)	60	104	0	0	14
3 oz of shellfish	9	84	3	0	100
3 oz hamburger	141	103	0	0	9
1 hot dog	119	21	0	0	6
2 c whole milk	74	32	46	0	291
1 c lowfat milk	23	34	48	0	308
2 slices white bread	20	19	110	0	71
1 c of potatoes (no additions)	1	8	65	0	7
12 oz can of beer	0	4	53	93	14
4 oz of wine	0	1	20	76	8
1 shot of liquor	0	0	0	106	0

[a] Visible fat *not* trimmed.

Appendix B

The table in Appendix B shows the results of fitting individual sources of calories (*i.e.*, the macronutrients fat, protein, alchol, and other carbohydrates) in multivariate logistic regressions that include total calories (as a single variable) as well as calcium and the nondietary risk factors.

When each macronutrient is fitted one at a time (Models A-D), only calories from carbohydrates produce a statistically significant improvement to the model (Model C − Model 3 [from Table 2] = 118.18 − 112.09 = 6.09). Specifically, Model C shows that the effect of carbohydrate on colon cancer is statistically significantly *different* from the 'average' effect of the other three macronutrients, while Model A shows that the effect of fat is not statistically significantly distinguishable from the 'average' effect of protein, carbohydrate, and alcohol. Models B and D show similarly that the effects of protein and alcohol, respectively, are not statistically significantly different from the 'average' effects of the remaining three macronutrients. However, these models do not provide a complete picture of the independent effects of these macronutrients adjusted for each other. Model 4 (in Table 2), in contrast, provides directly comparable estimates of the effects of these four components of total calories, each adjusted for the individual effects of the other components (as opposed to the 'average' effect of the other components). This is the reason we chose to present our results as in Table 2.

Table B1. Matched relative risks (RR)[a] and 95% confidence intervals (CI) for individual sources of calories (per 100 calories) after adjustment for total calories, calcium, and the nondietary risk factors

	All subjects (n = 746 pairs)		Males (n = 419 pairs)		Females (n = 327 pairs)	
	RR[a]	(CI)	RR[a]	(CI)	RR[a]	(CI)
Model A: The nondietary risk factors[b], calcium, plus...						
Total calories	1.03	(1.00-1.07)[c]	1.03	(0.99-1.07)	1.06	(0.99-1.13)[d]
Fat	1.02	(0.95-1.10)	1.05	(0.96-1.14)	0.96	(0.84-1.10)
Model A χ-square (df)	112.50	(10)	60.23	(6)	55.40	(10)
Model B: The nondietary risk factors[b], calcium, plus...						
Total calories	1.04	(1.01-1.06)[e]	1.04	(1.00-1.07)[c]	1.04	(0.99-1.09)
Protein	1.06	(0.88-1.28)	1.08	(0.86-1.36)	1.02	(0.73-1.48)
Model B χ-square (df)	112.49	(10)	59.54	(6)	55.10	(10)
Model C: The nondietary risk factors[b], calcium, plus...						
Total calories	1.08	(1.04-1.11)[f]	1.09	(1.05-1.14)[f]	1.03	(0.97-1.09)
Carbohydrate	0.93	(0.88-0.99)[c]	0.90	(0.84-0.97)[e]	1.02	(0.91-1.14)
Model C χ-square (df)	118.18	(10)	67.91	(6)	55.22	(10)
Model D: The nondietary risk factors,[b] calcium, plus...						
Total calories	1.04	(1.02-1.06)[f]	1.04	(1.01-1.06)[e]	1.04	(1.01-1.07)[c]
Alcohol	1.07	(1.00-1.14)[d]	1.07	(1.00-1.16)[d]	1.01	(0.86-1.19)
Model D χ-square (df)	115.84	(10)	62.85	(6)	55.11	(10)
Model E: The nondietary risk factors[c], calcium, plus...						
Total calories	1.01	(0.97-1.05)	0.99	(0.95-1.04)	1.06	(0.99-1.13)
Alcohol	1.09	(1.02-1.17)[c]	1.12	(1.10-1.22)[c]	1.00	(0.84-1.18)
Fat	1.06	(0.98-1.15)	1.11	(1.01-1.22)[c]	0.96	(0.84-1.10)
Model E χ-square (df)	118.26	(11)	67.50	(7)	55.40	(11)
Model F: The nondietary risk factors[b], calcium, plus...						
Total calories	1.02	(0.99-1.05)	1.02	(0.98-1.05)	1.04	(0.99-1.09)
Alcohol	1.08	(1.01-1.16)[c]	1.10	(1.01-1.19)[c]	1.01	(0.86-1.19)
Protein	1.13	(0.93-1.37)	1.19	(0.94-1.52)	1.02	(0.73-1.42)
Model F χ-square (df)	117.41	(11)	64.93	(7)	55.13	(11)
Model G: The nondietary risk factors[b], calcium, plus...						
Total calories	1.02	(0.99-1.05)	1.02	(0.98-1.05)	1.03	(0.98-1.09)
Alcohol	1.08	(1.01-1.16)[c]	1.09	(1.01-1.18)[c]	1.02	(0.86-1.20)
Saturated fat	1.13	(0.96-1.33)	1.15	(0.94-1.41)	1.04	(0.78-1.39)
Model G χ-square (df)	117.92	(11)	64.80	(9)	55.18	(11)
Model H: The nondietary risk factors[b], calcium, plus...						
Total calories	1.02	(0.98-1.06)	1.00	(0.96-1.05)	1.07	(1.01-1.15)[c]
Alcohol	1.08	(1.01-1.16)[c]	1.11	(1.02-1.21)[c]	0.98	(0.83-1.16)
Monounsaturated Fat	1.10	(0.91-1.34)	1.26	(0.99-1.60)[d]	0.82	(0.58-1.16)
Model H χ-square (df)	116.77	(11)	66.29	(7)	56.35	(11)
Model I: The nondietary risk factors[b], calcium, plus...						
Total calories	1.04	(1.00-1.07)[c]	1.02	(0.98-1.05)	1.07	(1.02-1.13)[e]
Alcohol	1.07	(1.00-1.15)[d]	1.10	(1.01-1.19)[c]	0.98	(0.83-1.16)
Polyunsaturated Fat	1.01	(0.78-1.31)	1.26	(0.90-1.77)	0.71	(0.45-1.10)
Model I χ-square (df)	115.84	(11)	64.73	(7)	57.54	(11)
Model J: The nondietary risk factors[b], calcium, plus...						
Total calories	1.07	(1.03-1.11)[f]	1.09	(1.04-1.14)[f]	1.03	(0.96-1.09)
Alcohol	1.03	(0.96-1.11)	1.02	(0.94-1.12)	1.03	(0.86-1.22)
Carbohydrate	0.94	(0.88-1.00)[b]	0.91	(0.84-0.99)[c]	1.03	(0.91-1.16)
Model J χ-square (df)	118.95	(11)	68.22	(7)	55.30	(11)

[a] Matched RRs per 100 calories (or, in the case of calcium, per 295 g), adjusted for all variables in the same model.
[b] Family history, weight, physical activity, and, if female, pregnancies (as four variables).
[c] P-value for trend < 0.05.
[d] P-value for trend < 0.10.
[e] P-value for trend < 0.01.
[f] P-value for trend < 0.001.

For comparison with results from other investigators, we also have included in the table for Appendix B other models in which *alcohol* and total calories are fitted together with various other macronutrients. Models E-J demonstrate that even after alcohol is included as a separate variable, no other single macronutrient, including the components of fat, represents a statistically significant *independent* risk factor. Carbohydrate is the macronutrient that comes closest to producing a statistically significant improvement to the model (*i.e.*, the closest to having an effect on colon cancer that is statistically significantly different from the effects of alcohol and the 'average' effect of fat and protein). In Model J, the effect of carbohydrate is of borderline significance ($P = 0.08$) while the effect of alcohol, which is statistically significant in models E through H, is not even close to being statistically significant. This is due in part to the fact that, even though the crude intakes of alcohol and carbohydrate are poorly correlated ($r = 0.05$), these two macronutrients are strongly negatively correlated once total calories are held constant (calorie-adjusted $r = -0.49$, $P < 0.0001$).