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Diet and Cancer of the Colon and Rectum: A Case-Control Study [1]

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ABSTRACT—In 1979-81, 419 patients with incident cases of colon and rectal cancer and 732 controls were questioned regarding diet and alcohol. Cancer cases were a population-based series reported to the South Australian Central Cancer Registry, were 30-74 years of age, and were residing in Metropolitan Adelaide. Controls were selected from the electoral roll and individually age- and sex-matched to cancer cases. The most consistent risk factor for colorectal cancer was dietary protein, which was associated with a twofold-to-threefold relative risk for colon cancer and for rectal cancer in women for all levels of consumption above the base line (i.e., the lowest consumption quintile). For male colon cancer the corresponding relative risk was similar; but for male rectal cancer, risk was elevated only at old ages. Total energy intake and, less clearly, meal frequency were also positively associated with increased risk. Total alcohol intake (but not specifically beer) was associated with increased risk of both colon and rectal cancer in women; in both sexes, there was an increased risk of colon and rectal cancer associated with spirits consumption. A reduced risk of rectal cancer was associated with vitamin C but not with vitamin A. The increased risk associated with high protein and total energy was confined to those consuming a low fiber diet, particularly among women; but some other aspects of the relationship between fiber consumption and risk of colorectal cancer were more complex. Some modifications and extensions of the current fat-to-bile acid-to-fiber theory of bowel carcinogenesis were suggested.—JNCI 1986; 76:557-569.

Previous studies of large bowel cancer [international correlation studies (*1*), case-control studies (*2-5*), and metabolic epidemiology (*6, 7*)], despite their inconsistent findings, have suggested a role for dietary factors in some stage of the cancer process. The currently prevailing model of colorectal carcinogenesis includes fat (*8, 9*) (associated with increased risk) and fiber (*8, 9*) (reduced risk) as well as a role for alcohol (*10-12*) (increased risk) and hormonal factors (*13-17*) each, partly or wholly, exerting influence via effects on hepatic and intestinal BA metabolism.

In previous studies, little attention has been paid to the possibility that relationships between risk and these dietary and hormonal factors may vary by site (colon vs. rectum) and within the colon by subsite, sex, and age. The arguments for considering these effects separately have been detailed elsewhere (*18*) but rest on the evidence for systematic variation in the age-sex-subsite distribution of bowel cancer and on the evidence for differences in etiology and perhaps histopathology of tumors from different subsites.

The present study investigated the relationship between nutrient intake and bowel cancer risk, including examination of postulated variations in diet-related risk by age, sex, and subsite (*13, 15*).

SUBJECTS AND METHODS

Subjects.—All those with newly incident cases of cancer of the colon and rectum who were reported to the South Australian Cancer Registry during 1979 and 1980, with additional inclusion of those with rectal cancer during early 1981, who resided in Metropolitan Adelaide, who were between the ages of 30 and 74 years, and who are alive at the time of reporting, made up the eligible case series. Of these 576 cases, 70 died before being contacted. Of the remaining 506, permission to interview was refused by the attending surgeon for 55 (10.9%), usually because the patient was terminally ill. Twenty-two (4.3%) refused to be interviewed and 10 (2.0%) were not found. To establish comparability with controls, the electoral roll status (*see further*) of the first 100 cases was determined. Of these, 99 were on the electoral roll.

Among controls there were 216 (20.4%) refusals, and 112 (10.6%) were not located out of a total of 1,060 eligible living individuals. Controls were selected from the Metropolitan Adelaide community via the electoral roll [voter registration is compulsory and more than 98% of those over 30 years of age are enrolled (*19*)]. Two controls were individually matched to each case by sex and age. The inclusion of the rectal cancer cases reported in early 1981 (37 males, 19 females) was undertaken to increase the number of rectal cancer cases to enable them to be studied as a separate cancer site. As no combined matched analyses were contemplated, these additional cases were each matched to 2 randomly selected controls for colon cases. Therefore, in the analyses that follow, the control populations for colon and rectum study contained 112 persons in common.

Data collection.—In all, 419 cases and 732 controls (*see* table 1) completed a self-administered dietary questionnaire and were interviewed regarding demographic variables, medical and family history, and dietary changes. Two trained interviewers—one male, one female—collected all information; each case-control triplet was interviewed by the same individual.

ABBREVIATIONS USED: BA = bile acid; CI = confidence interval; OR = odds ratio; RR = relative risk(s); VFA = volatile fatty acid(s).

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[3] We thank Ms. Sally Record for technical assistance with the computing; Ms. Maria Juras for interviewing; Dr. Anton Bonett, Central Cancer Registry of the South Australian Health Commission; and the many surgeons in Adelaide who facilitated the conduct of the study.

TABLE 1.—*Study population: Age, sex, and site distribution of cases and controls*

Age, yr	Colon				Rectum			
	Males, No.		Females, No.		Males, No.		Females, No.	
	Cases	Matched controls	Cases	Matched controls	Cases	Matched controls	Cases	Matched controls
30–54	20	35	21	40	15	33	19	43
55–59	17	39	13	30	27	55	16	26
60–64	29	49	15	28	27	60	12	33
65–69	28	59	18	32	26	43	16	25
70–74	27	59	32	67	29	57	12	21
Total[a]	121	241	99	197	124	248	75	148

[a] As described in the text, there is some overlap between colon and rectum control groups.

The dietary questionnaire, a quantitative food-frequency questionnaire developed by our research group, has been used extensively in a variety of settings and has been tested for repeatability and against biochemical measures (*20–22*). Recent evidence suggests that, in general, food frequency questionnaires provide reliable and repeatable data (*22–24*). The version used recorded frequency of consumption of 141 food items, as well as alcohol consumption and a variety of qualitative questions regarding cooking methods, fat use, bread type, etc., which were used in deriving nutrient indices.

Where changes had occurred recently, respondents (both cases and controls) were asked to describe their diets as they had been 12 months prior to interview. This procedure was to preclude, in unbiased fashion, those who had changed after diagnosis and treatment. Usual diet was asked for to preclude changes in diets that had resulted from symptoms. It was decided that interviews were to be conducted in the home rather than in the hospital to allow resumption of usual dietary (and other) habits and to ensure that there was comparability in the interview setting between cases and controls. Cases were contacted after they had been reported to the cancer registry. Mean time from operation to interview was 9.1 ± 0.1 months.

Food frequency data were converted to nutrient consumption via FREQUAN (*21*) by using food table data [based on the McCance and Widdowson data base (*25*) modified where appropriate and possible with local nutrient analyses] and standard serve sizes (*26*). No direct comparisons between the sexes were planned or undertaken, so the use of a single serve size created no additional problems.

During the latter part of the study, 106 cases and 222 controls were specifically questioned regarding recent changes in diet. Twenty-seven cases (25.5%) and 28 controls (12.6%) indicated that their present diets had changed in the previous 12 months. These 2 groups were compared with all cases and all controls, respectively. The difference between the females in this "changed" group and the study as a whole were minimal and tended to make the results reported somewhat conservative. The reverse was true for the male "changed" group where the differences were also greater.

Cancers were all histologically confirmed and only adenocarcinomas were included. They were categorized by subsite according to the International Classification of Diseases (Ninth Revision) and aggregated for some analyses into proximal colon (cecum, ascending colon, hepatic flexure), distal colon (transverse colon to sigmoid), and rectum (including rectosigmoid).

Demographic data, including usual occupation as a measure of social class, were collected at interview.

Presentation of analyses.—Analyses were presented initially as comparisons of means and as matched OR (approximating RR) and 95% confidence intervals. For the dietary variables, exposure was categorized into quintiles based on the total study population; a conditional logistic regression model was used to determine the OR associated with each quintile (*27*). To control for the simultaneous effects of several variables, the data were analyzed either stratified on potential confounders or by the use of conditional logistic regression models (*27*).

RESULTS

Means.—The mean consumption levels of major nutrients thought to be relevant to the genesis of large bowel cancer are shown in table 2. For colon cancer in women, mean consumption of most nutrients, including fiber, was statistically significantly higher in cases than in controls. For male colon cancer, the differences between cases and controls in consumption of saturated fat, total energy, and alcohol approached statistical significance. These observations were also generally consistent with those for rectal cancer, although there appeared to be even less of a difference in consumption between male cases and controls. Expressed as a percentage of total energy intake, there were no differences in intakes of nutrients between cases and controls in either sex, with the exception of alcohol consumption, which was higher in female colon cancer cases than in controls.

Major nutrients; colon.—The combined population of cases and controls formed the basis for stratification into exposure quintiles separately for males and females. The quintiles were approximately one step apart for males and females for most nutrients: i.e., in absolute consumption terms, the "base-line" quintile in males

TABLE 2.—*Colorectal cancer: Mean ± SEM daily consumption of nutrients*

Nutrient	Colon						Rectum					
	Males			Females			Males			Females		
	Cases, n=121	Controls, n=241	P	Cases, n=99	Controls, n=197	P	Cases, n=124	Controls, n=248	P	Cases, n=75	Controls, n=148	P
Protein, g	95.5±2.4	93.8±2.0	.306	84.8±2.1	78.9±1.5	.012	91.4±2.5	90.5±1.7	.384	85.1±3.2	77.2±2.2	.020
Fat, g	113.5±3.7	108.0±2.7	.116	89.2±3.0	83.8±1.8	.062	110.7±4.3	104.5±2.4	.106	91.6±3.9	82.5±2.8	.028
Saturated fat, g	46.8±1.7	44.1±1.1	.091	37.3±1.4	35.2±0.9	.097	46.4±1.9	43.0±1.0	.058	38.2±1.8	34.4±1.3	.044
Cholesterol, mg	418.9±14.9	413.0±14.7	.390	326.3±12.3	300.9±8.7	.047	405.5±16.4	384.8±10.6	.138	319.7±16.2	300.4±11.9	.172
Energy, MJ[a]	10.5±0.3	10.0±0.2	.084	8.4±0.2	7.8±0.1	.010	10.2±0.3	9.8±0.2	.155	8.5±0.3	7.6±0.2	.003
Fiber, g	20.2±0.7	20.3±0.6	.952	22.4±0.8	19.7±0.6	.009	19.7±0.7	20.0±0.5	.381	21.7±1.0	19.4±0.6	.044
Alcohol, g	22.4±2.6	17.7±1.5	.063	6.8±1.1	4.3±0.6	.020	18.5±2.1	19.2±1.5	.387	6.7±1.4	5.4±0.8	.200

[a] MJ=1 kilocalorie×0.004184.

approximated the second quintile in females. The only major exception to this was fiber, where male and female absolute intakes were similar (*see* table 3).

Table 3 shows the relationship between exposure quintiles of major nutrients and risk of colon cancer. For males, there was a consistent elevation of RR associated with protein consumption above the base line. For females, protein and total energy consumption showed a stepwise increase in RR for the first quintile of exposure above the base line but no further increase. Fat, saturated fat, and cholesterol showed a similar pattern. For alcohol in women, there may be a similar, but less marked, increase at the fourth exposure quintile. Fiber consumption was associated with an increasing estimate of RR for each quintile of exposure. Analyses with nutrients expressed as a percentage of total energy intake were less clear and showed few differences between cases and controls.

TABLE 3.—*Colon cancer and diet—univariate matched RR (95% CI) by exposure quintiles*

Nutrient	RR (95% CI) for quintile:[a]				
	1	2	3	4	5
Males					
Protein	1.0	2.2 (1.0–4.8)	2.3 (1.1–4.8)	1.9 (0.9–4.0)	2.1 (1.0–4.5)
Fat	1.0	1.0 (0.5–2.1)	1.0 (0.5–2.2)	1.2 (0.6–2.4)	1.4 (0.7–2.9)
Saturated fat	1.0	0.6 (0.3–1.3)	1.3 (0.7–2.6)	1.3 (0.7–2.6)	1.1 (0.6–2.3)
Cholesterol	1.0	1.5 (0.7–3.2)	1.0 (0.5–2.0)	1.6 (0.8–3.2)	1.5 (0.7–3.0)
Energy	1.0	1.1 (0.5–2.3)	1.6 (0.8–3.2)	1.3 (0.7–2.6)	1.8 (0.9–3.7)
Alcohol	1.0	0.6 (0.3–1.3)	0.4 (0.2–1.0)	0.8 (0.4–1.7)	1.0 (0.5–2.1)
Fiber	1.0	1.2 (0.6–2.4)	2.1 (1.0–4.3)	1.0 (0.5–2.1)	1.3 (0.6–2.6)
Females					
Protein	1.0	2.6 (1.1–6.1)	2.1 (0.9–5.0)	2.2 (1.0–4.9)	2.8 (1.5–5.2)
Fat	1.0	1.9 (0.8–4.3)	1.9 (0.8–4.5)	1.8 (0.6–5.2)	1.7 (0.8–3.6)
Saturated fat	1.0	1.6 (0.7–3.7)	2.4 (1.0–5.5)	1.0 (0.4–2.4)	2.1 (0.9–4.8)
Cholesterol	1.0	2.0 (0.8–4.7)	2.2 (1.0–5.3)	1.3 (0.6–2.8)	2.7 (1.2–6.1)
Energy	1.0	6.2 (2.1–18.0)	3.4 (1.1–9.8)	5.3 (1.8–15.7)	4.8 (1.7–13.9)
Alcohol	1.0	1.4 (0.7–2.7)	1.2 (0.5–2.6)	2.0 (0.9–4.4)	2.0 (0.9–4.5)
Fiber	1.0	1.8 (0.7–4.3)	2.2 (0.9–5.4)	2.9 (1.3–6.8)	4.1 (1.7–10.0)

[a] Quintile cut points—for males: protein (g/day): 68.4, 81.4, 94.8, 113.8; fat (g/day): 76.9, 91.4, 110.6, 136.8; saturated fat (g/day): 29.7, 37.8, 46.2, 57.5; cholesterol (mg/day): 247.0, 327.0, 426.0, 533.0; energy (MJ/day): 7.6, 9.0, 10.5, 12.2; alcohol (g/day): 0.1, 4.0, 12.8, 31.8; fiber (g/day); 13.2, 17.1, 21.2, 26.8. Quintile cut points—for females: protein (g/day): 60.5, 71.2, 84.5, 97.5; fat (g/day): 59.5, 75.1, 89.0, 108.6; saturated fat (g/day): 24.1, 30.9, 37.6, 47.0; cholesterol (mg/day): 204.0, 257.0, 311.0, 395.0; energy (MJ/day): 6.0, 7.2, 8.3, 9.6; alcohol (g/day): 0.01, 0.95, 3.9, 12.9 (the 38% nondrinkers comprise the lowest quintile; the remaining cut points are at 55, 70, and 85% of the distribution); fiber (g/day): 14.0, 17.9, 21.0, 25.7.

As modifying effects of age had been postulated and, specifically, as the possibility that dietary factors may differ in their relative influence before and after menopause in women (*13, 15*), patterns of differences in dietary intakes were investigated between cases and controls at various ages. It was found that the youngest cases of colon cancer in women had low intakes of fiber compared with intakes of controls but that older cases showed both higher mean intakes and greater variability than did respective controls. This pattern was confined to women with distal (transverse to sigmoid) colon cancer (data not shown separately), the sex-subsite group that largely accounted for the association between increased RR and higher fiber consumption overall.

On the basis of these observations the question arose as to what, among other measured variables, distinguished females who were low fiber consumers from females who were high fiber consumers. It was striking that, although other nutrients increased approximately linearly as fiber intake increased among controls, the same was not true for cases. In cases, low fiber consumption was associated with consumption of other major nutrients at a level approaching that of those in the highest fiber intake group; the lowest intake of other nutrients was found among the "middle fiber" intake group of cases. Thus the case-control differences in consumption of major nutrients and energy were largely confined to those women who had low intakes of fiber. Nondietary variables did not distinguish between low and high fiber-consuming groups of women. Table 4 shows the estimates of RR associated with tertiles of consumption of major nutrients after stratifying on tertiles of fiber per megajoule of energy (to control for the association between amounts of fiber and total energy in the diet).

For females, there was a gradient of increased RR with increasing consumption of total fat, saturated fat, and protein at low consumption levels of fiber. This finding also indicated, however, that there was the same unexpected increase in RR associated with increasing consumption of fiber as seen in table 3, even after controlling for total energy intake.

For males, the first of these two observations holds—namely, that a higher estimate of RR was associated with higher consumption of nutrients at lower levels of fiber intake; but there was also evidence that a reducing risk was associated with increasing fiber at high levels of nutrient intake.

The overall pattern associated with age suggested that dietary-related RR were more marked at young ages in women and at older ages in men [for details, *see (18)*].

Major nutrients; rectum.—Table 5 shows the corresponding findings for rectal cancer cases and controls. For males, there was no significant variation from 1.0 associated with any major nutrient. Alcohol consumption was unexpectedly associated with a nonsignificant reduction in RR for all categories of drinker. For females, protein, total fat, saturated fat, and total dietary energy were associated with increases in RR with increasing levels of consumption. The top 20% of the

TABLE 4.—*Colon cancer and diet: RR (95% CI) associated with tertiles of major nutrients after stratification on fiber intake controlled for total energy intake*

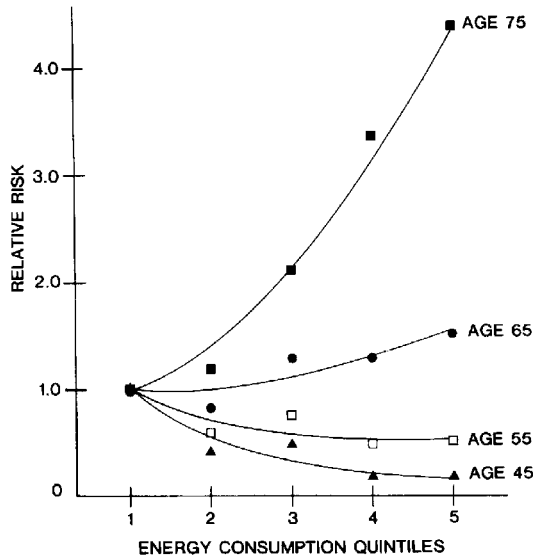
Nutrient	Level	Fiber per MJ of energy		
		Low	Mid	High
Females				
Protein	Low	1.0	0.5 (0.1-2.7)	1.3 (0.3-5.0)
	Mid	0.6 (0.1-3.0)	3.3 (0.9-11.8)	3.8 (1.1-12.9)
	High	2.3 (0.7-7.4)	1.7 (0.5-6.3)	2.3 (0.6-8.4)
Total fat	Low	1.0	1.6 (0.3-7.3)	2.7 (0.7-10.6)
	Mid	1.7 (0.4-7.8)	2.8 (0.7-11.1)	3.2 (0.8-12.6)
	High	2.4 (0.6-9.0)	2.1 (0.5-8.9)	3.1 (0.7-14.0)
Saturated fat	Low	1.0	2.1 (0.4-12.1)	3.2 (0.7-15.2)
	Mid	2.1 (0.4-11.1)	3.8 (0.8-18.3)	6.0 (1.3-27.4)
	High	3.2 (0.7-14.8)	2.3 (0.4-12.3)	2.3 (0.4-13.8)
Males				
Protein	Low	1.0	0.8 (0.2-2.7)	1.3 (0.4-3.8)
	Med	1.3 (0.4-4.2)	1.7 (0.6-5.1)	1.5 (0.5-4.7)
	High	1.6 (0.5-4.6)	1.6 (0.5-4.9)	1.1 (0.3-3.7)
Total fat	Low	1.0	1.2 (0.4-3.6)	1.5 (0.5-4.3)
	Med	1.5 (0.5-4.6)	1.9 (0.7-5.3)	1.9 (0.7-5.6)
	High	2.1 (0.8-5.7)	1.8 (0.6-5.1)	1.0 (0.3-3.5)
Saturated fat	Low	1.0	1.4 (0.4-5.5)	2.6 (0.8-8.5)
	Med	3.5 (1.0-12.3)	2.8 (0.9-9.1)	2.5 (0.7-8.9)
	High	3.3 (1.0-10.3)	4.0 (1.2-13.4)	2.3 (0.6-8.9)

consumption distributions of almost all of these variables was associated with a doubling or greater RR of rectal cancer.

Stratification on age suggested little variation of RR of rectal cancer for women but showed a marked interaction of most nutrient consumption levels with age for men. Text-figure 1 shows relative risks at various ages derived from fitting the total energy consumption levels

TABLE 5.—*Rectal cancer and diet: Univariate matched RR (95% CI) by exposure quintiles*

Nutrient	RR (95% CI) for quintile:				
	1	2	3	4	5
Males					
Protein	1.0	0.9 (0.4-1.9)	1.3 (0.7-2.6)	1.1 (0.6-2.2)	1.0 (0.5-1.9)
Fat	1.0	0.7 (0.4-1.6)	1.8 (0.9-3.6)	1.1 (0.6-2.2)	1.3 (0.7-2.6)
Saturated fat	1.0	1.3 (0.6-2.6)	1.6 (0.8-3.2)	1.2 (0.6-2.5)	1.7 (0.9-3.4)
Cholesterol	1.0	1.3 (0.7-2.7)	1.2 (0.6-2.3)	1.1 (0.6-2.0)	1.2 (0.6-2.4)
Energy	1.0	0.8 (0.4-1.7)	1.2 (0.6-2.4)	1.0 (0.5-2.0)	1.2 (0.6-2.4)
Fiber	1.0	1.2 (0.6-2.5)	0.7 (0.3-1.3)	0.5 (0.3-1.1)	1.3 (0.6-2.7)
Alcohol	1.0	0.7 (0.3-1.3)	0.8 (0.4-1.5)	0.6 (0.3-1.2)	0.7 (0.4-1.5)
Females					
Protein	1.0	2.5 (1.0-6.7)	2.3 (0.9-6.1)	2.1 (0.7-6.1)	3.0 (1.2-7.6)
Fat	1.0	3.2 (1.2-8.4)	3.1 (1.1-8.4)	3.6 (0.9-13.8)	2.5 (1.1-6.0)
Saturated fat	1.0	2.7 (1.0-7.1)	2.1 (0.9-5.2)	1.8 (0.7-4.6)	2.3 (1.0-5.4)
Cholesterol	1.0	1.5 (0.6-3.5)	0.7 (0.3-1.9)	1.6 (0.7-4.0)	1.4 (0.6-3.2)
Energy	1.0	2.4 (0.9-6.7)	1.2 (0.5-3.4)	2.6 (0.9-7.1)	4.6 (1.7-12.5)
Fiber	1.0	1.4 (0.6-3.5)	0.9 (0.3-2.3)	1.2 (0.5-3.2)	2.4 (1.0-5.7)
Alcohol	1.0	0.6 (0.2-1.3)	1.7 (0.7-3.9)	1.1 (0.5-2.5)	1.5 (0.6-3.7)



TEXT-FIGURE 1.—Estimates of matched RR for male rectal cancer associated with quintiles of total energy consumption at various ages (yr). Estimates are derived from a conditional logistic regression model that incorporated the primary variables (energy consumption quintiles) and age-interaction terms. Smoothed curves are for clarification of relationships only.

TABLE 6.—*Colon and rectal cancer and micronutrients: Univariate matched RR (95% CI) by exposure quintiles by sex*

Nutrient	RR (95% CI) for quintile:[a]				
	1	2	3	4	5
Male colon					
β-carotene	1.0	0.6 (0.3–1.5)	0.2 (0.4–1.5)	0.8 (0.4–1.6)	0.8 (0.4–1.6)
Vitamin C	1.0	1.2 (0.6–1.3)	1.5 (0.8–3.1)	1.8 (0.9–3.8)	1.0 (0.5–2.1)
Retinol	1.0	1.1 (0.6–2.3)	1.5 (0.7–2.9)	1.1 (0.5–2.1)	1.4 (0.8–2.4)
Female colon					
β-carotene	1.0	0.8 (0.4–1.6)	1.4 (0.5–3.5)	0.9 (0.4–2.0)	2.2 (1.0–4.7)
Vitamin C	1.0	1.4 (0.6–3.2)	1.2 (0.6–2.6)	1.3 (0.6–2.9)	2.2 (1.0–4.8)
Retinol	1.0	1.0 (0.4–2.1)	1.1 (0.5–2.4)	1.0 (0.5–2.2)	1.6 (0.7–3.5)
Male rectum					
β-carotene	1.0	0.9 (0.4–1.7)	1.1 (0.6–2.2)	0.5 (0.2–1.1)	0.9 (0.4–1.7)
Vitamin C	1.0	0.7 (0.4–1.4)	0.7 (0.4–1.4)	0.6 (0.3–1.2)	0.6 (0.3–1.1)
Retinol	1.0	0.8 (0.4–1.4)	0.7 (0.3–1.3)	0.8 (0.4–1.6)	0.7 (0.4–1.4)
Female rectum					
β-carotene	1.0	0.9 (0.4–2.2)	0.9 (0.3–3.2)	1.2 (0.5–3.0)	1.5 (0.6–3.6)
Vitamin C	1.0	0.4 (0.1–1.0)	0.8 (0.3–1.7)	0.9 (0.4–2.4)	0.3 (0.1–0.8)
Retinol	1.0	1.0 (0.4–2.3)	1.5 (0.7–3.4)	1.2 (0.5–2.7)	1.3 (0.6–3.0)

[a] Quintile cut points—for males: β-carotene (μg/day): 2,360, 3,560, 4,770, 7,000; vitamin C (mg/day): 59.6, 104.5, 158.5, 223.0; retinol (μg/day): 300, 446, 816, 1,436. Quintile cut points—for females: β-carotene (μg/day): 2,970, 4,290, 5,750, 8,180; vitamin C (mg/day): 72.8, 127.0, 178.0, 255.0; retinol (μg/day): 252, 379, 585, 1,410.

and age interaction terms in a logistic model. The pattern was consistent for each nutrient, including fiber and alcohol, with higher consumption of each associated with reduced RR at younger ages but with markedly increased RR at older ages. The net effect across all ages combined was no apparent relationship between nutrient consumption levels and risk of rectal cancer as seen in table 5. However, the observed pattern was consistent in both age-stratified analyses (not shown) and fitted models and was therefore not simply artifactually produced by the constraints of the fitted model. The confidence limits were wide and tended to include 1.0, except for higher consumption at older ages.

Micronutrients.—Consumption of some specific micronutrients (vitamin C, β-carotene, retinol) showed little relationship to risk of colon cancer in either sex; for rectal cancer there was a reduction in RR associated with vitamin C in both sexes but more marked in women (*see* table 6). In male rectal cancer, stratification by age showed that vitamin C consumption was particularly associated with reduced RR at younger ages, this effect disappearing only by 70 years of age. This pattern was consistent, however, with that for major nutrients noted above (*see* text-fig. 1) and may reflect only that young male rectal cancer cases appeared to eat much less than did either older cases or controls. However, no marked increased was observed in RR associated with high consumption of vitamin C at older ages.

Fiber source.—Table 7 shows that the increased RR associated with higher levels of consumption of dietary fiber in women was confined primarily to consumption of cereal fiber. Furthermore, the increased risk was confined to the distal colon (data not shown separately) and rectum.

Alcohol source.—Table 8 shows the RR associated

TABLE 7.—*Colon and rectal cancer and fiber consumption: Univariate matched RR (95% CI) by exposure quintiles*

Fiber source	RR (95% CI) for quintile:				
	1	2	3	4	5
Male colon					
Vegetable fiber	1.0	1.2 (0.6–2.5)	2.0 (0.9–4.1)	1.2 (0.6–2.5)	1.3 (0.6–2.6)
Cereal fiber	1.0	1.5 (0.8–2.9)	1.3 (0.6–2.6)	1.2 (0.6–2.4)	1.4 (0.7–2.8)
Female colon					
Vegetable fiber	1.0	1.1 (0.5–2.5)	1.4 (0.7–3.0)	0.8 (0.3–1.8)	1.7 (0.8–3.6)
Cereal fiber	1.0	3.1 (1.3–7.9)	2.0 (0.8–5.3)	4.6 (1.9–11.3)	5.1 (2.1–12.7)
Male rectum					
Vegetable fiber	1.0	1.1 (0.6–2.1)	0.8 (0.4–1.6)	0.6 (0.3–1.2)	0.9 (0.4–1.8)
Cereal fiber	1.0	1.3 (0.6–2.6)	1.8 (0.9–3.7)	1.6 (0.8–3.3)	1.2 (0.6–2.3)
Female rectum					
Vegetable fiber	1.0	0.5 (0.2–1.1)	0.5 (0.2–1.3)	0.6 (0.3–1.4)	0.7 (0.3–1.5)
Cereal fiber	1.0	2.7 (1.0–7.3)	1.3 (0.5–3.8)	2.3 (0.9–6.0)	4.4 (1.7–12.0)

TABLE 8.—*Colon and rectal cancer and alcohol: Matched univariate RR and 95% CI by alcohol type*

Source	β	χ^2	RR[a]	95% CI
Male colon[b]				
Beer	−0.00	0.00	1.00	0.99–1.01
Wine	0.02	0.93	1.02	0.98–1.06
Spirit	0.08	9.33	1.08	1.03–1.13
Female colon[b]				
Beer	0.01	0.06	1.01	0.95–1.06
Wine	0.04	2.06	1.04	0.98–1.11
Spirit	0.13	4.51	1.13	1.01–1.27
Male rectum[c]				
Beer	−0.00	0.30	1.00	0.98–1.01
Wine	−0.02	1.42	0.98	0.95–1.01
Spirit	0.04	3.67	1.04	1.00–1.09
Female rectum[b]				
Beer	−0.03	1.06	0.97	0.92–1.03
Wine	0.11	5.22	1.11	1.02–1.22
Spirit	0.05	0.67	1.05	0.94–1.17

[a] RR expressed/glass/wk.
[b] These results are essentially unaltered when all three exposures are included in a single model.
[c] Inclusion of all three alcohol variables for male rectum in a single model raises RR (95% CI) for spirit consumption to 1.05 (1.01–1.10).

with alcohol consumption expressed per glass per week for both colon and rectum. Only spirits consumption was associated with increased RR at each site, significantly so in three of four sex-site categories. For colon cancer, these figures indicated approximately a doubling of risk for a glass per day of spirits in women and for two glasses per day in men. There was no association, in these data, between beer consumption and risk at either site. Separate analyses by subsite within the colon showed that the RR of distal colon cancer, the numerically predominant subsite, accounted for most of the above-mentioned risk variation and that risk of proximal (cecum and ascending) colon cancer was unrelated to alcohol consumption.

Eating frequency.—Table 9 shows the relationship between eating frequency (number of times per day, irrespective of size of meal) and RR of colon and rectal cancer, after controlling for total energy intake. There may be an increase of risk of colon, but not rectal, cancer associated with higher frequency of eating.

TABLE 9.—*Colon and rectal cancer and diet: Conditional logistic regression models; meal frequency (controlling for total energy intake) by sex*

Daily meal frequency	RR	95% CI
Male colon		
≤3	1.0	
4	1.3	0.7–2.4
≥5	1.6	0.9–2.7
Female colon		
≤3	1.0	
4	0.8	0.4–1.6
≥5	1.7	0.9–3.1
Male rectum		
≤3	1.0	
4	1.1	0.6–1.8
≥5	1.3	0.8–2.1
Female rectum		
≤3	1.0	
4	1.0	0.5–2.0
≥5	1.0	0.6–1.9

TABLE 10.—*Male colon cancer: Conditional logistic regression model*[a]

Variable	β	χ^2	RR	95% CI
Protein quintiles				
1			1.0	
2	0.78	3.39	2.2	1.0–5.0
3	1.04	6.73	2.8	1.3–6.2
4	0.76	3.40	2.2	1.0–4.8
5	0.91	4.40	2.5	1.1–5.8
Fiber per MJ of energy quintiles				
1			1.0	
2	−0.07	0.03	0.9	0.4–2.0
3	0.01	0.00	1.0	0.5–2.1
4	−0.28	0.44	0.8	0.3–1.7
5	0.10	0.06	1.1	0.5–2.4
Spirits consumption[b]	0.08	7.42	1.08	1.02–1.15
Occupation				
Professional and/or managerial			1.0	
Other	−1.17	16.06	0.3	0.2–0.6

[a] Overall risk function: Likelihood ratio, $\chi^2_{10}=36.01$; $P<.0001$.
[b] RR expressed/glass/wk.

Combined models.—Tables 10 and 11 show logistic regression models detailing the association between nutrients and RR of colon cancer controlling in women for reproductive variables (*16*) and in men for socioeconomic status, which proved to be a significant explanatory variable. All variables in these models are shown.

Colon cancer.—In summary, this study found that, for colon cancer, protein was the major nutrient associated

TABLE 11.—*Female colon cancer: Conditional logistic regression model*[a]

Variable	β	χ^2	RR	95% CI
Protein quintiles				
1			1.0	
2	0.97	4.34	2.6	1.1–6.6
3	0.77	2.57	2.2	0.8–5.5
4	1.16	6.19	3.2	1.3–8.0
5	1.35	7.08	3.9	1.4–10.4
Fiber per MJ of energy quintiles				
1			1.0	
2	−0.25	0.27	0.8	0.3–2.0
3	0.93	3.10	2.5	0.9–7.2
4	0.57	1.56	1.8	0.7–4.3
5	0.68	2.06	2.0	0.8–5.0
Spirits consumption[b]	0.12	2.96	1.12	0.98–1.28
OC use (mo)				
0			1.0	
1–24	0.77	1.75	0.5	0.2 1.5
≥25	−1.42	2.93	0.2	0.1–1.2
Parity				
0			1.0	
1–2	−0.16	0.16	0.9	0.4–1.9
≥3	−1.07	6.42	0.3	0.2–0.8

[a] Overall risk function: Likelihood ratio $\chi^2_{13}=36.97$; $P=.0004$.
[b] RR expressed/glass/wk.

with increased RR in both sexes, showing about a doubling of risk in males and about a twofold-to-fourfold increase in females for the four upper quintiles relative to the lowest.

Age interacted with nutrient consumption so that the effect for males tended to be greater at older ages (the greatest RR was associated with total energy), whereas, for females, for left colon cancer and for the colon as a whole, RR estimates were higher at younger ages [*see* (*18*)].

Increased intakes of total fat, saturated fat, cholesterol, and total energy were more clearly associated with increased RR in females.

The increase in RR estimates for fiber exposure, particularly in women, was due partly to the complex relationship that fiber and energy bore to each other. The increased RR estimates for energy and protein, etc., are only evident at low fiber intake, but there was also an association between increasing fiber consumption and increasing estimates of RR.

Micronutrients did not appear to be related to the risk of colon cancer.

Overall, alcohol was associated with increases in RR of colon cancer in women but not in men. However, when analyzed by alcohol type, consumption of spirits was associated with about a 10% increase in RR per glass per week for both sexes.

Rectal cancer.—Protein, fat, saturated fat, and total energy were each associated with increased RR of rectal cancer in females consistently across all age groups and in males at older ages. Vitamin C was associated with a reduced RR of rectal cancer in women at all ages and in men until around 60 years of age. Spirits consumption in males and wine in females were associated with an increase of 5–10% in RR per glass per week.

At young ages, there was an increased RR of rectal cancer in males associated with a generalized low dietary intake. One possible interpretation of this was that protective factors such as vitamin C (and possibly fiber) were critically reduced by low total intakes at young ages. The crossover from reduced RR to increased RR at high consumption occurred a decade later for vitamin C than for the major nutrients; vitamin C was not associated with significantly increased RR, even at 75 years of age.

DISCUSSION

There are a series of issues that this study raises, the first items of which are methodologic.

This is the first community-based case–control study of large bowel cancer to be reported. Previous studies have relied on hospital cases (exclusively) and hospital controls (all studies except one). The use of a population-based cancer registry for cases and a population register for controls eliminates several of the biases inherent in hospital-based studies, particularly studies of dietary etiology; diets postulated to be related to colon cancer are also thought to bear on the risk of many other chronic diseases. Even traffic crashes (alcohol) and conditions such as osteoarthritis (obesity) are not free of this potential.

The dietary method chosen for this study is one that is well established for etiologic studies of cancer—a food frequency method (20–24). The use of standard serve (rather than self-described) sizes results in some misclassification and thus biasing of the RR toward 1.0. The method, in addition to satisfactory repeatability characteristics, is consistent with "common-sense" checks such as women reporting lower total consumptions than men and older persons reporting less total consumption than younger. Repeatability data suggest that even reports of past dietary patterns though "contaminated" by current practice allow ready differentiation into groups (*22*). Note was taken of the extent to which the presence of disease altered the current dietary practice. The inclusion of those whose diet had changed recently (both cases and controls) tended to bias the RR estimates toward 1.0 in women, arguing that the above estimates for women are somewhat conservative. The reverse, however, was true for the males.

Fat, protein, total energy, and meal frequency.—A central finding of this study is that total energy or protein or some other nutrient for which these are good markers in this study population (e.g., fat and saturated fat) are associated with increased risk of large bowel cancer—a finding consistent with the prior hypothesis and previous work. The judgment as to which nutrient is the relevant one, however, is very much determined by the biologic model invoked to explain the development of the disease; fat or saturated fat have usually been considered the most likely, since they stimulate increased BA excretion with subsequent initiation or promotion of a mucosal cancer (*8, 9*).

The absence of a monotonic dose-response effect both of protein (but *see* table 11) and of energy in relation to colon cancer indicates the possibility of a risk saturation point with at least 80% of the population exceeding it (*18, 28*). Factors other than diet, particularly genetic susceptibility, and, in women, reproductive behavior will therefore determine the additional individual variation in likelihood of developing colon cancer. We have discussed more extensively elsewhere the possible relevance of dose-response relationships and the problem of categorization of universal exposures (*18*). A linear dose-response relationship is only one of various possible and plausible models. The major argument for its applicability to cancer biology appears to rest only on crude analogy with pharmacologic and toxicologic models.

The only previous study in which the role of specific nutrients, as opposed to food groups, was able to be considered concluded that, on the strength of the relationships between RR estimates and dietary constituents, saturated fat was the most likely major dietary constituent to be part of the causal chain (*5*). That study expressed the results in terms of tertiles of exposure and presented them separately for males and females and for colon and rectum. The major methodologic difference

between that study and this present one was the use of 2 control groups in the former study—one hospital group and one neighborhood group. They found RR for the highest tertile of saturated fat consumption compared with the lowest of approximately 2.5 for men and women.

Two earlier studies (*3, 4*)[4] had described a relationship between frequency of consumption of foods high in saturated fat and increased risk of large bowel cancer. Haenszel et al. (*29*) (studying the Hawaiian Japanese), Bjelke in Norway (*2*), and Phillips (*3*) each describe an association between meat consumption and risk. Several studies, however, have failed to find such a relationship.

Both nutrients and individual foods, while perhaps important in their own right, are also acting as markers for dietary intake in general. In the international correlation studies, no study has examined the relationship between mean energy intake and colon cancer; the commonest finding is a relationship between increased risk and consumption of animal protein, fat, and meat (*1*), these variables being closely correlated with each other and with total energy intake.

In examining smaller agglomerations of populations, e.g., States of the United States (*30*), United Kingdom, United States, Australia, and New Zealand over time (*31*), the relationship with these variables has not emerged as strongly. Liu et al. (*32*) have suggested cholesterol as the candidate exposure. Less direct evidence from earlier case-control studies concerns the relationship of nonmeat protein consumption—nutmeat, milk, fish—to *reduced* risk (*3*).

Most of the animal experiments and the human metabolic epidemiology have focused on the fat-BA model, with little attention paid to the possible role of protein or overall food intake. Reddy et al. (*33*), however, noted that high protein in the diet of rats, irrespective of source, is associated with elevated levels of bacterial β-glucuronidase activity in the large intestine, one of the enzymes postulated as relevant to the bile acid theory. Reddy et al. (*34*) have shown similar effects in humans on high meat vs. low meat diet. More recently, Wise et al. (*35*) have shown that dietary protein levels influence several bacterial enzymes, postulated to be relevant to bowel carcinogenesis, in the rat cecum.

Reddy et al. (*36*) have further shown that carcinogenesis is more likely to occur on a high fat, high protein diet than a low fat, low protein diet, irrespective of the fat and protein source. Topping and Visek (*37*) have shown that of rats fed 7.5% (low) dietary protein fewer than half developed tumors compared with those fed higher protein diets (15 or 22% protein) and that tumor numbers per rat were only 50% of that in the other 2 groups. (There was no evidence of a dose-response effect in relation to protein exposure in this animal experiment.) However, a high protein, low fat experiment has not been conducted.

[4] Phillips' criteria (*3*) for "high-saturated fat foods" are not defined; Dales et al. (*4*) used the criteria of foods containing ≥5% saturated fat.

Fiber.—There are several possibilities in relation to the apparent implausibility of an increased intake of dietary fiber itself being part of a causal chain leading (directly or indirectly) to increased risk of large bowel cancer.

One possibility is that the dietary instrument used varies in its capacity to provide an accurate picture of nutrient consumption. The data on repeatability (*22, 28*) do indeed suggest that dietary fiber is not as consistently reported as, e.g., alcohol or fat. However, this kind of essentially random inaccuracy ought to produce a conservative, but not reversed, estimate of the RR associated with that variable; there is no a priori reason to believe that this dietary misclassification might differ between cases and controls.

Another possibility is that cases may well have (in some instances, are known to have) increased their fiber intake postoperatively on the advice of their surgeon. This would indeed produce exactly the pattern noted, inasmuch as cases would be more likely to have an increased intake of fiber. However, *both* cases and controls were asked to describe their intake as it had been 12 months earlier if they had changed it either as a result of recent illness or for some other reason. As noted in "Subjects and Methods," only marginal differences were seen between those (both cases and controls) who had changed their diets recently and the rest of the population. Further, it was reasoned that the only increase in dietary fiber likely to be recommended would be the addition of bran to the daily intake. A variable—"fiber minus bran"—behaved in almost identical fashion to "all fiber"; bran accounted for very little of total dietary fiber intake (0.5–1.0% in males, 1.0–3.6% in females).

Lyon et al. (*38*) have recently argued that as numerous major nutrients, especially fat, protein, and fiber, are highly correlated with total energy intake, then, if cases consume more food than controls, each of these nutrients will be associated with increased RR. Thus, while only guilty by association, a putative protective factor may appear to increase the risk.

It was considered, reasoning as had Lyon (*38*), that the most likely explanation for increased risk associated with fiber was that total dietary fiber intake is closely associated with total food intake. Several other studies of free-living Australian populations (*20*) have shown intake of dietary fiber to be correlated with total energy intake. If, as in this study, total energy intake is associated with increased risk of bowel cancer, the increased risk associated with fiber is likely a problem of multicollinearity, the fiber merely acting as a marker for total energy or other major nutrient intakes.

Fiber from vegetable and cereal sources were considered in separate analyses. There appears to be little relationship between fiber consumption of both kinds and risk of colon cancer in males (and little difference between subsites). For females, cereal fiber is associated with increased risk and in dose-response fashion. This result is largely explained by its strong positive association with risk of distal colon cancer.

Despite our result appearing to be paradoxic for die-

tary fiber, it may cast some light on previously puzzling findings, which have been ignored in other studies.

The two studies of Haenszel et al. (*29, 39*) found an increased RR for colon cancer associated with high rice consumption in Japanese both in Japan and Hawaii. They comment on this finding on *both* occasions, only to say that it runs counter to the known low colon cancer risk of rice-eating populations. Despite their low risk, Japanese consume levels of fiber almost identical with this Australian population (*40*). Wynder et al. (*41*) found fruit intake to be associated with an increased RR of colorectal cancer, and Haenszel et al. (*29*) found legumes (particularly string beans) to be a risk factor. Martinez et al. (*42*) found an increasing RR of large bowel cancer associated with increasing fiber consumption and considered recall bias as a possible explanation.

Hill et al. (*43*) noted that dietary fiber and total dietary intake, as well as fat intake, increase with income in the Hong Kong population and that this in turn is positively associated with increasing risk of colorectal cancer. Although several correlation studies have found negative relationships between risk and cereal or fiber consumption (*44, 45*), the consistent "protective" factor in analytic studies has been vegetables rather than cereals. Thus Stocks (*46*), Bjelke (*2*), Phillips (*3*), Graham et al. (*47*), and Haenszel et al. (*39*) describe reduced risks associated with some variety of vegetable foods. Modan et al. (*48*) and Dales et al. (*4*) constructed high-fiber indices that showed a protective effect against large bowel cancer, but the overwhelming majority of the dietary constituents in these indices were vegetable rather than cereal. Further, of Modan's 73 high fiber items (≥0.5% of fiber), four were consumed *more* often by cases than by both sets of controls. Two of these were bourghul (cracked wheat) and oats (*48*). Jain et al. (*5*) found no relationship between *crude* fiber intake and risk of colorectal cancer.

Thus the finding in this present study, that cereal fiber is associated with increased risk of colon cancer in women, is not inconsistent with previous analytic studies, though it differs from popular belief and current hypotheses. In summary, the important observations on fiber are these: 1) High fiber consumption is associated with increased estimates of RR for colon cancer, particularly in women; and, within this group, it is particularly associated with risk of distal colon cancer and possibly only at older ages. 2) The relationship between fiber intake and consumption of other nutrients is complex among female cases but not among controls (and not among male cases and controls); female cases who consume low fiber also consume high intakes of other nutrients and food in general. Thus the increased estimates of RR for large bowel cancer observed for the female population as a whole were shown to be largely explained by the increased RR in those with a low fiber intake. 3) If there is *any* real increase in RR associated with high fiber consumption in women (independent of this complex relationship with other nutrients or total energy), then it is confined to an association with cereal fiber.

The differences between men and women with regard to fiber-related risk may partly reflect more accurate responses from women. The complex relationship between total energy and fiber noted above for women argues against its being a sole explanation; findings from several human and animal studies are relevant: Bowel transit time, fecal weight, and aspects of fecal biochemistry (e.g., pH) are each related to dietary fiber intake and have each been shown to vary between the sexes even when diets were controlled (*15*); cereal fiber has been shown to provoke cell proliferation differentially within the rat colon (*49*) and to enhance carcinogenesis (*50*); cellulose is associated with a distal shift and older age at appearance of tumors (*51, 52*).

Differences by age.—This study provides information on the way in which age interacts with dietary exposures. The interaction is with age at presentation (not age at, e.g., initial exposure) and therefore may reflect a relationship between dietary exposures and a critical exposure time *or* between such exposures and the biologic behavior of a cancer (perhaps, e.g., accelerating or retarding the rate of growth between transformation and clinical presentation).

The most striking feature related to the age interaction is the fact that, in fitted models (and in age-stratified analyses), the strength of the relationships between dietary exposures and risk of colon cancer is greater in women that are younger but in men that are older [for details *see* (*18*)].

Colon cancer has an overall sex ratio of around 1.0 but a female colon cancer excess for those between 25 and 55 years of age (*13, 15*). A higher risk at younger ages in relation to dietary exposures for women and the reverse for men is consistent with this overall pattern of colon cancer incidence.

One study (*53*), which has investigated both age and sex in the 1,2-dimethylhydrazine-induced rat model of large bowel carcinogenesis, found that males were approximately equally susceptible to developing bowel cancer at several ages while females had both lower incidence overall and declining susceptibility with age. Castration of males produced a susceptibility pattern similar to that of the females, while castration of females had no effect on age-related susceptibility (*53*). These age-sex patterns are also consistent with those noted in the present study for colon cancer.

For rectal cancer, age-associated risk for dietary variables is maximal at older ages in males and unaffected in females. This finding too is consistent with the descriptive epidemiology for rectal cancer, where the sex ratio is around 1.0 at younger ages but increases steadily with age, suggesting perhaps that older males are more susceptible to cumulative insults whether due to dietary or other exposures.

Micronutrients.—Vitamin C (*2*) and vitamin A (*54*) indices (constructed with reference to foods high in these micronutrients) have been postulated to be related to reduced risk of epithelial cancers as well as specifically cancer of colon and rectum. In the present study, vitamin C is associated with reduced estimates of RR for

rectal cancer but no association is noted between either micronutrient and risk of colon cancer.

Jain et al. (*5*) failed to find a consistent relationship between vitamin C exposure and risk of colorectal cancer. DeCosse et al. (*55*) have described a decreased incidence of rectal polyps following vitamin C administration to patients with familial polyposis. Bruce et al. (*56*) noted a reduction of fecal mutagens as a consequence of vitamin C administration. Possible mechanisms are not established, but vitamin C is an antioxidant and is also known to reduce the absorption of nitrosamines (*56*).

Alcohol and beer.—In view of the extensive literature on the possible relationship between beer and, particularly, rectal cancer (*10–12*), the failure to find a relationship in this population is puzzling. Seven previous case-control studies have collected data on alcohol consumption; three of these found a relationship. A study in alcoholics (*57*) and a follow-up study in Norway (*58*) have also showed an excess rectal cancer risk for beer drinkers, but possibly no more marked than that for spirits drinkers. Of the two follow-up studies of brewery workers, one showed a relationship to rectal cancer (*11*) while the other did not (*59*).

No study has found a negative relationship between beer consumption and risk of colorectal cancer. Thus it may be that differences in the beer itself (brewing practices, other constituents) may be significant in determining risk; it may also be, however, that characteristics of the study design itself (e.g., the quality of the instrument) determine whether a relationship is detected.

In this study, a consistent colorectal cancer relationship was noted not specifically with beer but with spirits.

Tuyns et al. (*60*) have reported a slightly, but not significantly, elevated RR of rectal cancer in association with alcohol consumption; Wynder and Shigematsu (*61*) noted a higher percentage of heavy drinkers among male rectal cancer cases than among one of their control groups, but much of this appears to be due to differences in beer consumption. Modan et al. (*48*) described colon cancer cases as consuming a significantly different amount of alcohol from controls but specified neither the direction of this difference nor the beverage types involved.

The relationship between RR and alcohol consumption appears, as with most other dietary variables, to be stronger for colon cancer in females than in males. In regard to the reasons, similar considerations to those already examined for diet may be canvassed for the differences for alcohol.

However, females report consumption at lower levels than males; thus, even if males are misreporting their consumption overall, it still may be that women are more sensitive to the effects of alcohol on risk of large bowel cancer. This approach would be consistent with other observations about male-female responses to alcohol (*62*).

Nutrients, alcohol, and large bowel cancer; conclusions.—In the light of the findings discussed above, it is proposed that the fat-BA theory is incomplete and that this present study provides some evidence for a more extensive multifactorial hypothesis.

In addition to the role of fat (and possibly protein) stimulating BA production and in addition to fiber as a BA-sequestering agent and bacterial substrate (thus producing VFA and altering gut pH), a role is proposed for total dietary intake (including feeding frequency), for alcohol, and for sex hormone differences. Vitamin C is proposed as a protective agent against rectal cancer.

The level of total dietary intake is suggested to influence the rate of colon cell renewal and therefore to influence the rate at which cell transformation or at which malignant progression is likely to occur. Further, the frequency of feeding influences the profile of circulating BA—increased feeding frequency will increase the recirculation of the BA pool and thus the proportion of secondary BA.

Against this background, BA production will be influenced particularly by fat (and possibly protein), alcohol, female sex hormones, and possibly other endogenous influences producing a BA profile that has both long-term features and short-term fluctuations. Menopause will alter hormone levels—one long-term influence. BA profile will have a greater influence on proximal colon, but this effect will be reduced more distally where the general background stimulation associated with total dietary intake will be more important (*63*).

Low protein intake may improve the capacity of the liver to deal with exogenous carcinogens (*64*).

Fiber intake will exert several influences. In the presence of high energy (and fat) intake, low fiber will be associated with an increased risk, both as a consequence of increased BA exposure for the colon mucosa and the reduced VFA production; the VFA would normally act as differentiating agents for the colon cells, lower gut pH, and therefore reduce the effectiveness of BA-degrading bacterial enzymes (*65*).

High fiber intake may influence colon cell turnover rates proximally but not distally, in the same way that it does in rats.

In a susceptible population (and this may be tested by a longitudinal study), high fiber intakes will delay the appearance of cancer, thus being associated with paradoxic increase in (particularly distal) tumors among the old.

Female sex hormones influence not only BA production but other aspects of gut physiology, so that the female colon is more susceptible to dietary-associated carcinogenesis at a younger age. In addition to the established effects on transit time, fecal bulk, and pH, one should consider that bacterial populations may be directly influenced by female hormones, as may colon mucosal cells.

Rectal carcinoma will be influenced in part by the biologic and chemical activity of the fecal mass, therefore by some of the above factors (but probably not by VFA and pH), and also by the integrity of the mucosal cells that may be influenced by micronutrients, particularly by vitamin C.

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