Dietary Calcium, Vitamin D, and the Risk of Colorectal Cancer in Stockholm, Sweden[1]

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Abstract

The epidemiology of large bowel cancer suggests an etiological role for dietary factors. Although the evidence is inconsistent, several studies have suggested an inverse association between dietary vitamin D or calcium and colorectal cancer risk.

We conducted a population-based case-control study to examine the relationship between dietary vitamin D and calcium and colorectal cancer among residents of Stockholm, Sweden.

Between January 1986 and March 1988, 352 cases of colon cancer and 217 cases of rectal cancer diagnosed among living persons residing in Stockholm County were identified via a cancer surveillance network established among all the hospitals in Sweden and the Stockholm Regional Cancer Registry. Controls (512) were randomly selected from a computerized population registry. Dietary intake was assessed using a quantitative food frequency questionnaire focusing on average consumption during the preceding 5 years. Supplemental intake of vitamin D and calcium was not ascertained. Logistic regression was used to calculate odds ratios (ORs) as the measure of association between the exposure of interest (vitamin D or calcium) and cancer risk.

Increasing levels of dietary vitamin D were inversely associated with the risk of colorectal cancer. The association was somewhat more pronounced for cancers of the rectum [OR, 0.5; 95% confidence interval (CI), 0.3–0.9 between the highest and lowest quartiles] than for cancers of the colon (OR, 0.6; 95% CI, 0.4–1.0) after adjustment for age, sex, and total caloric and protein intake. Dietary calcium was not associated with the adjusted risk of colon (OR, 1.2; 95% CI, 0.7–2.1) or rectal cancer (OR, 1.0; 95% CI, 0.5–1.9). Further adjustments for fat and dietary fiber intake, body mass index, and physical activity had little or no effect on the results.

These results suggest that dietary vitamin D may reduce the risk of large bowel cancer, particularly rectal cancer. In addition, although some of the previous data suggested a protective effect for calcium against cancers of the large bowel, we could not document such an effect.

Introduction

Colorectal cancer is the second leading cause of cancer-related deaths worldwide, with clear evidence of environmental determinants, especially diet (1). Although the specific nutrients linking diet to the risk of colorectal cancer have yet to be established, high intake of animal fat or protein and low intake of fruits and vegetables have repeatedly been shown to increase the risk of this malignancy (1). It is thought that fat promotes large bowel cancer by increasing the levels of free ionized fatty acids and unconjugated bile acids, which are irritating and toxic to the surrounding epithelium, in the bowel lumen.

Dietary calcium may protect against the cancer-promoting effects of dietary fat by binding with and reducing the concentrations of free fatty acids and bile in the lumen of the bowel (2). The demonstration in animal models that calcium reduces bowel epithelial damage from instilled neutral fats and bile acids provides some empirical support for this hypothesis (3). The epidemiological evidence, however, is inconsistent. Several, but not all, epidemiological studies have reported an inverse association between dietary calcium or dairy products and the risk of colorectal cancer (4–19). Vitamin D has received less attention in this regard, but there are suggestions that it may also be associated with a decreased risk of colon cancer (4, 14, 17, 19, 20).

In an effort to elucidate these issues, we present here the results of a population-based case-control study designed to examine a number of potential dietary risk factors for colorectal cancer, including calcium and vitamin D.

Subjects and Methods

The association between calcium and vitamin D and the risk of large bowel cancer was investigated as part of a case-control study of colorectal cancer conducted in Stockhom, Sweden during the period 1986–1988 (21–24). The study base included all subjects born in Sweden between 1907 and 1946 living in Stockholm County during part or all of the observation period January 22, 1986, to March 15, 1988. Cases (histologically confirmed adenocarcinoma of the colon or rectum, first diagnosed during the observation period) were identified via a surveillance network established at the local hospitals in Stockholm County and through the Stockholm Regional Cancer Registry. Potential controls were randomly selected every 4 months during the study period from the computerized popu-

Received 2/13/96; revised 8/12/96; accepted 8/14/96.

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[1] This work was supported by a Scholar Award from the American Cancer Society (to J. A. B.) and Grants 2228-B86-013XA and 2228-B87-02XA from the Swedish National Cancer Society (to M. G. d. V.).

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lation registry within sex and four strata of year of birth (1907–1916, 1917–1926, 1927–1936, 1937–1946).

Information regarding diet, height, weight, and other personal characteristics was obtained from study subjects by means of a questionnaire. Area hospitals were visited weekly by a research assistant who handed out the questionnaire to potential cases. Patients who were too ill to complete the questionnaire themselves were aided by the assistant. Cases identified through the Regional Cancer Registry (19%), and all controls, were mailed an identical questionnaire after receiving an introductory letter and telephone call. If necessary, a telephone interview was used to obtain missing information from participants. Surrogate respondents were not used for subjects who died or who were too ill to participate.

The questionnaire included quantitative food frequency items, focusing on average consumption of 55 food items during the preceding 5 years, excluding periods of altered diet due to illness. The food items, including cheese and ice cream, were chosen to represent more than 80% of the foods in the Swedish diet. Response alternatives were never, less than 1 time per month, 1–3 times per month, 1–4 times per week, and more than 4 times per week. Information on portion size was also requested as "small," "standard," or "large" using a photographic guide. In addition, each study participant provided information on the number of servings of regular and skim milk, yogurt, and fil (a milk-like beverage favored in Sweden) consumed in a week. Additional questions regarded height and weight 5 years prior to the study. Other items focused on occupational and recreational exercise, and the two exercise responses were combined into a single scale: very active (very active in work and/or recreation), moderately active (moderately active, but not very active, in work and/or recreation), and inactive (inactive in both work and recreation). The use of supplemental calcium and vitamin D was not ascertained.

From the data provided, intake of total energy, fat, fiber, protein, calcium, and vitamin D was computed using the nutrient data base at the Swedish National Food Administration. The total amount of milk-like products consumed in one week was taken as the sum of the number of servings of milk, yogurt, and fil. These variables were divided into quartiles based on the distribution of intake among the controls. Body mass index [weight (kg)/height (m^2)] was based on weight 5 years ago and was similarly categorized into quartiles based on the distribution among the controls.

ORs[3] were used as the measure of association between the exposures of interest (calcium intake or vitamin D intake) and the risk of colorectal cancer. These were calculated using likelihood ratio techniques with unconditional logistic regression using the Stata statistical package (College Station, TX). In the analyses, calcium and vitamin D consumption were considered separately as categorical and linear variables. The categories were selected based on the distribution of intake among controls. All ORs were adjusted for age (eight categories) and sex. In addition, the ORs were adjusted for the following risk factors, which were previously shown to be associated with the risk of colorectal cancer in this data set: total energy intake, total fat intake, total protein intake, total dietary fiber intake, body mass index (21), and physical activity (22). These variables were entered as categorical variables. Possible effect modification was considered by fitting separate models for each sex, age group (≤69 and >69), and quartile of fat intake. The statistical significance of the effect modification was considered by introducing interaction terms between categories of exposure into the logistic models and examining the associated change in deviance. Finally, in separate models, the consumption of dairy products was considered as the exposure of interest.

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 1 Characteristics of cases and controls

	Rectal cancer	Colon cancer	Controls
Number	217	352	512
% female	50.7	53.7	53.9
Age (yr)	66.9 ± 8.5[a]	68.4 ± 8.9	67.7 ± 9.0
Energy intake (kcal/day)	1834 ± 580	1816 ± 580	1727 ± 524
Protein intake (g/day)	68.8 ± 22.2	67.4 ± 22.0	62.8 ± 22.5
Fat intake (g/day)	68.3 ± 25.3	67.7 ± 24.7	63.3 ± 24.6
Carbohydrate intake (g/day)	223 ± 75	221 ± 73	213 ± 64
Calcium intake (mg/day)	943 ± 363	933 ± 360	865 ± 344
Vitamin D intake (μg/day)	5.02 ± 2.8	4.88 ± 2.74	4.93 ± 4.24

[a] Mean ± SD.

Results

A total of 452 cases of colon cancer, 268 cases of rectal cancer, and 624 controls were identified for participation in the study. The nonresponse rate was 22% among potential cases (25 refused, 32 disabled, 79 dead, 15 not located, and 10 incomplete answers) and 19% among potential controls (79 refused, 24 disabled, 3 dead, 6 not located, and 7 incomplete answers), leaving 352 cases of colon cancer, 217 cases of rectal cancer, and 512 controls for analysis. Characteristics of the cases and controls are summarized in Table 1.

There was no association between vitamin D consumption and the age- and sex-adjusted risk of either colon cancer (OR, 1.0; 95% CI, 0.7–1.6 for highest *versus* lowest quartile) or rectal cancer (OR, 1.1; 95% CI, 0.7–1.8; Table 2). However, after further adjustment for total energy and protein intake, increased vitamin D intake was associated with a decreased risk of colorectal cancer. The associations were somewhat stronger for rectal than for colon cancer. Compared to the lowest quartile, subjects in the highest quartile of vitamin D intake had a 50% decrease in the odds of rectal cancer (OR, 0.5; 95% CI, 0.3–0.9) and a 40% decrease in the odds of colon cancer (OR, 0.6; 95% CI, 0.4–1.0). Further adjustments for fat and dietary fiber intake, body mass index, and physical activity had little or no effect on the results.

We next examined whether the association between vitamin D and diet-adjusted cancer risk was modified by age, sex, or level of dietary fat intake. The inverse relationship between vitamin D and the risk of colon and rectal cancer were broadly similar in older and younger subjects (Table 3). On the other hand, for both cancers of the colon and rectum, the associations were stronger for women (OR for cancer of the colon, quartile IV *versus* quartile I, 0.4; 95% CI, 0.2–0.9; OR for cancer of the rectum, 0.3; 95% CI, 0.1–0.8) than for men (OR for colon, 0.9; 95% CI, 0.4–1.8; OR for rectum, 0.8; 95% CI, 0.3–1.8). For rectal cancer, the inverse association between vitamin D and cancer risk did not differ by the level of dietary fat intake. However, there was a suggestion that colon cancer risk was modified by dietary fat. Among subjects with low fat intake, there was no association between vitamin D and the risk of colon cancer (OR, 1.0; 95% CI, 0.4–0.9), whereas there was a 60% decrease in cancer risk among subjects with a high fat intake (OR, 0.4; 95% CI, 0.2–0.9). None of the corresponding

Table 2 ORs and 95% CIs for risk of colorectal cancer associated with intake of vitamin D and calcium

Exposure	No. of		Colon cancer		No. of cases	Rectal cancer	
	Controls	Cases	OR (95% CI)[a]	OR (95% CI)[b]		OR (95% CI[a]	OR (95% CI)[b]
Vitamin D							
≤2.8 μg/day	129	84	1.0	1.0	51	1.0	1.0
2.9–4.2 μg/day	119	72	0.9 (0.6–1.4)	0.8 (0.5–1.2)	46	0.9 (0.6–1.5)	0.7 (0.4–1.3)
4.2–6 μg/day	137	109	1.2 (0.8–1.8)	0.9 (0.6–1.4)	60	1.1 (0.7–1.7)	0.7 (0.4–1.2)
≥7 μg/day	127	87	1.1 (0.7–1.6)	0.6 (0.4–1.0)	60	1.1 (0.7–1.8)	0.5 (0.3–0.9)
			P^c = 0.939	P = 0.076		P = 0.57	P = 0.083
Calcium							
≤640 mg/day	128	65	1.0	1.0	43	1.0	1.0
641–825 mg/day	128	82	1.2 (0.8–1.9)	1.2 (0.7–1.8)	39	0.9 (0.6–1.5)	0.8 (0.5–1.4)
826–1056 mg/day	129	94	1.4 (0.9–2.1)	1.2 (0.7–1.9)	66	1.6 (1.0–2.5)	1.3 (0.7–2.3)
≥1057 mg/day	127	111	1.7 (1.2–2.5)	1.2 (0.7–2.1)	69	1.6 (1.0–2.5)	1.0 (0.5–1.9)
			P = 0.016	P = 0.621		P = 0.042	P = 0.729

[a] Adjusted for age and sex.
[b] Adjusted for age, sex, and total energy and protein intake.
[c] Determined by test of trend.

Table 3 ORs and 95% CIs for colorectal cancer comparing highest to lowest quartiles of dietary vitamin D and calcium by age group, sex, and dietary fat

Exposure	No. of		Colon cancer, OR (95% CI)[a]		No. of cases	Rectal cancer, OR (95% CI)[a]	
	Controls	Cases	Vitamin D	Calcium		Vitamin D	Calcium
Age ≤69 years	257	171	0.5 (0.2–1.0)	1.2 (0.6–2.5)	119	0.5 (0.2–1.1)	0.6 (0.3–1.4)
Age >69 years	255	181	0.8 (0.4–1.5)	1.4 (0.6–3.0)	98	0.5 (0.2–1.2)	1.9 (0.7–5.0)
Male	236	163	0.9 (0.4–1.8)	1.6 (0.7–3.7)	107	0.8 (0.3–1.8)	1.0 (0.4–2.5)
Female	276	189	0.4 (0.2–0.9)	1.0 (0.5–2.0)	110	0.3 (0.1–0.8)	0.9 (0.4–2.1)
Fat ≤59 g/day	250	146	1.0 (0.4–2.4)	0.7 (0.3–1.6)	80	0.5 (0.1–1.7)	0.7 (0.2–2.1)
Fat >59 g/day	262	206	0.4 (0.2–0.9)	1.8 (0.8–4.0)	137	0.5 (0.2–1.1)	0.9 (0.4–2.1)

[a] Adjusted for age, sex, and total energy and protein intake.

interaction terms introduced into the various logistic models were significant, however.

Dietary calcium was associated with an increased age- and sex-adjusted risk of both colon cancer (OR, 1.7; 95% CI, 1.2–2.4 for highest *versus* lowest quartile) and rectal cancer (OR, 1.6; 95% CI, 1.0–2.5 for highest *versus* lowest quartile). Additional adjustment for total energy and protein intake, however, produced risk estimates closer to unity (OR for colon, 1.2; 95% CI, 0.7–2.1, and OR for rectum, 1.0; 95% CI, 0.5–1.9 for highest *versus* lowest quartile). Analyzed as a continuous variable, calcium intake increased the risks of colon and rectal cancer by factors of 1.1 (95% CI, 0.9–1.2) and 1.0 (95% CI, 0.9–1.2) for each 250-mg increase in dietary calcium. The results were virtually identical when body mass index, physical activity, dietary fat, and dietary fiber were included as covariates. Among older and younger subjects, the association of calcium and cancer risk was similar for colon cancer but differed for rectal cancer (Table 3). Among subjects ≤69 years, the OR of rectal cancer for the highest intake of calcium (*versus* lowest) was 0.6 (95% CI, 0.3–1.4), whereas for those older than 69 years it was 1.9 (95% CI, 0.7–5.0). The risk estimates for colon or rectal cancer did not differ by sex or dietary fat.

We also examined whether the risk of colorectal cancer was associated with particular foods rich in calcium and/or vitamin D. There was no substantial association between milk and milk-like products and the combined risk of colorectal cancer after adjusting for total energy and protein intake (OR for highest *versus* lowest quartile, 1.1; 95% CI 0.7–1.6). Similarly, heavy consumers of either ice cream or cheese were not at altered risk. The OR for >4 servings of ice cream/week *versus* none was 1.4 (95% CI, 0.7–3.1), and the OR for >4 servings of cheese/week *versus* <4 servings/week was 1.0 (95% CI, 0.8–1.4).

Finally, there was no evidence of mutual confounding among the exposures investigated. In multivariate models including calcium and vitamin D, the ORs for the exposures under study were essentially unchanged from the preceding analyses (data not shown).

Discussion

In this population-based case-control study, there were suggestions that vitamin D consumption was inversely related to the age-, sex-, and diet-adjusted risk of colorectal cancer. Across the extreme quartiles of intake, vitamin D was associated with a 40 and 50% decrease in the risk of colon and rectal cancer, respectively. On the other hand, there was no association of calcium and the age-, sex-, and diet-adjusted risk of large bowel cancer.

The epidemiological data on calcium and vitamin D and colorectal cancer risk vary. Ecological data has shown generally higher calcium consumption in countries with a lower incidence of colorectal cancer (25), but in these analyses the number of data points was small, and this design cannot lead to firm conclusions. One of the earliest analytical epidemiological studies to note an inverse association between calcium and the risk of large bowel cancer was the prospective Western Electric study (4). Several other studies have also noted an inverse

association (7, 8, 10, 11), whereas others found only a weak, statistically insignificant association (5, 6, 9, 17, 19) or no association at all (12–16, 18) .

Garland *et al.* (4) were also the first to suggest that vitamin D may exert a protective effect on the subsequent development of colon cancer. In the Western Electric study, there was a 45% reduction in the risk of colon cancer across the extreme quartiles of vitamin D intake. Subsequently, a nested case-control analysis of these data showed an inverse relationship between increasing serum 25-hydroxyvitamin D concentrations and the risk of colon cancer (20). In a case control study from Spain (14) and the Iowa Women's Health Study (17), an insignificant reduction in the risk of colorectal cancer was noted among subjects with the highest consumption of vitamin D. On the other hand, no association between vitamin D and colorectal cancer risk was found in other epidemiological studies (11, 16, 19). Only two of these studies examined the combined end point of colorectal cancers (4, 14); both reported an apparent protective effect.

Aside from issues of confounding and bias, the apparent differences in these various studies may simply reflect the methodological difficulty of determining the contribution of specific micronutrients to cancer risk. The complex interaction among a large number of micronutrients and foods makes it difficult to isolate the effect of a specific micronutrient from the more general effects of a particular food or dietary pattern. Whether dietary vitamin D itself is protective for colorectal cancer or whether it is simply a surrogate marker for a particular protective dietary pattern in this study is uncertain.

Furthermore, these conflicting reports about the effect of vitamin D and the risk of large bowel cancer may be explained in part by differences in endogenous levels of vitamin D generated by sunlight exposure. Because we did not account for this other source of vitamin D in our study, we are unable to eliminate confounding as an explanation for our findings.

The apparent lack of a protective effect of calcium warrants further comment. If not due to chance or response bias, it may be related to the levels of calcium intake recorded in this study. The average intake of calcium in the highest quartile in this data set (*i.e.*, 1376 mg/day) is below that which some suggest is required for a protective effect (*e.g.*, 1500 mg/day or more; Ref. 26) However, other studies that have reported a beneficial effect of calcium have had a range of intakes comparable to those of our subjects. Because nondietary sources of calcium, particularly supplementation, were not accounted for in this study, it is likely that we have underestimated total calcium consumption. If the use of calcium supplements varied by case-control status, this may have led to a distorted estimate of the effect of calcium.

In summary, our findings indicate that dietary vitamin D may be protective against colorectal cancer but that calcium seems not to be. Whether this reflects a stronger and perhaps specific effect of vitamin D on cancer risk or the problems of data analysis resulting from collinearity of micronutrients and selected foods is unclear. Randomized controlled trials are probably needed to establish whether these nutrients affect the risk of colorectal neoplasia.

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