The Role of Chronic Constipation, Diarrhea, and Laxative Use in the Etiology of Large-Bowel Cancer

Data from the Melbourne Colorectal Cancer Study

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Life-long bowel habits of 685 colorectal cancer cases and 723 age/sex frequency matched community controls were investigated as one part of a large, comprehensive, population-based study of colorectal cancer incidence, etiology, and survival, The Melbourne Colorectal Cancer Study. Self-reported chronic constipation was statistically significantly more common in cases than in controls ($P = .05$). Three or more bowel actions per day were reported by more cases than controls but the total number of respondents in this subset consisted of only ten cases and two controls. Otherwise, the frequency and consistency of bowel motions was similarly distributed among cases and controls. Constipation disappeared as a significant risk when simultaneously adjusted for previously determined dietary risk factors, indicating that it is the diet and not the constipation that is associated with the risk of large-bowel cancer. Additionally, a highly statistically significant association ($P = .02$) was found with the risk of colorectal cancer in those who reported constipation and also had a high fat intake, a finding consistent with current hypotheses of colorectal carcinogenesis. It is concluded that chronic constipation, diarrhea, and the frequency and consistency of bowel motions, as well as laxative use, are unlikely to be etiologic factors in the development of colorectal cancer. Self-reported chronic constipation is a marginally significant indicator of excess risk of large-bowel cancer and may be used as one of the indices in the screening of individuals for this cancer. [Key words: Colorectal cancer; Bowel habit; Constipation; Diarrhea; Laxatives; Etiology; Screening; Epidemiology]

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THIS REPORT EXAMINES the associations between colorectal cancer and bowel habit in data drawn from a large, population-based study of large-bowel cancer incidence, etiology, and survival, The Melbourne Colorectal Cancer Study.[1,2] The main hypothesis tested in relation to bowel habit was that constipation (which may be an indicator of slow intestinal transit) is a risk factor in the subsequent development of colorectal cancer.[3] A secondary hypothesis was that laxative use is a risk for colorectal cancer.[4]

Materials and Methods

The data on bowel habit were drawn from the case control arm of the Melbourne Colorectal Cancer Study.[1,2] The case control study examined all the major current hypotheses of colorectal cancer risk, cause, and protection, including bowel habits.

The cases constituted all histologically confirmed new patients with colorectal adenocarcinoma diagnosed in the 12-month period between April 1980 and April 1981 who were usual residents of Metropolitan Melbourne, which had a population of 2.81 million at the time of the study.[1,2] Patients with a past history of ulcerative colitis or familial polyposis (ten patients) were excluded from the case control study in order to examine a population that was likely to be a homogeneous etiologic entity.

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Community controls who were age/sex frequency matched with the cases were randomly selected from the same geographic area as the cases, according to a cluster sampling plan devised by the Australian Bureau of Statistics, the Government Agency responsible for the Australian Population Census, and other vital statistics. The demographic characteristics by age, sex, country of birth, and religion of both patients and controls (and of site and subsite for patients) not included in the study were analyzed in comparison with those included.[1,5,6] It was concluded that selection/exclusion bias was not a significant factor[1,5,6] and, for brevity, these data are not described again.

Two questionnaires were administered by personal interview. The first questionnaire contained data on age, sex, country of birth and religion, current and past illnesses, operations, medications, bowel habit and laxative use, psychosocial and stress factors, parity, and family history data. The second interview was the dietary questionnaire, which included questions on alcohol intake and tobacco use. In preliminary feasibility and pilot studies,[1] it was difficult to gather accurate data on bowel habit, and several different approaches were tried before the final format of the questions was arrived at. This part of the interview was extensive and detailed and dealt with bowel habit over the entire adult life of the respondent regarding "constipation," "diarrhea," frequency and consistency of bowel motions, and laxative use. It was uniformly introduced by the interviewer in the following way: "Now I would like to ask you a few questions about your bowels." For patients only, the following sentence was then added: "The questions apply to *before* your present trouble started. First, I'd like to talk to you about constipation, by which I mean having trouble moving your bowels, or moving your bowels less frequently than usual, with smaller and harder motions than usual. I'm referring to before your *present* trouble started. Have you in your adult life been constipated, excluding when this occurs only once or twice a year or when you are on holidays?" For those who responded "yes" to this question, the following was then asked: "How often did this constipation occur, when did it first start and for how long did it last? Over the years, have you ever had bouts of diarrhea, that is, passed frequent watery motions which lasted longer than a week? I mean, apart from gastroenteritis or food poisoning episodes." The frequency of bowel actions was recorded and for bowel action consistency, all respondents were shown a card with four diagrams, labeled: 1—liquid; 2—does not hold shape, would form a mound; 3—holds shape, sausage shaped, firm; 4—small pellets, hard. In relation to laxative use, the following was asked, "In order to make your bowels move or for any other reason, have you ever taken laxatives more frequently than every month in your adult life?" For

patients, the following was also added: "I am talking about taking laxatives *before* your present trouble started." It was pointed out in this question that the interviewer was talking about commercially produced laxatives and not the nutritional or home remedy types, such as bran, hot water, orange juice, etc.

The data analysis was made by unconditional logistic regression[7] using the GLIM Statistical Package.[8] The estimates of relative risk (RR) were tested for statistical significance expressed as chi square variables written χ^2_n where n is the degrees of freedom (df). Cross tabulations were made using SPSSx.[9]

Results

In the case control study, there were 715 patients and 727 age/sex frequency matched controls. For the investigation of bowel habit, 22 metachronous colorectal cancers were excluded because these patients had had bowel resections in the past that may have altered their bowel habit. In eight further patients and in four controls, data on bowel habit were missing and these were also excluded. Thus, the analysis that follows refers to 685 cases and 723 controls. Among patients, there were 375 colon cancers and 310 rectal cancers. The age distribution for male patients, female patients, male controls, and female controls was remarkably similar to the mean age of the whole group, which was 65 years (standard deviation, 11).

Self-Reported Bowel Habit: Table 1 indicates the frequencies, relative risks and statistical significance of self-reported constipation, diarrhea, and laxative use. Chronic constipation episodes, as defined in the study, were reported by 215 patients (31 percent) and 191 controls (26 percent) and this difference was statistically significant (P = .05). Further analysis of self-reported constipation indicated that there was a statistically significant excess of those reporting constipation among males, those who were less than 65 years old, and those who had colon cancer (Table 1). Episodes of self-reported diarrhea and the use of commercial laxatives were similarly distributed between patients and controls (Table 1).

Two previous studies of apparently healthy populations have found that at least 95 percent of adults have a bowel movement frequency of between three per day and three per week.[10,11] Thus, it was decided to analyze the data on self-reported frequency of bowel motions for the ten and 20 years prior to the interview in the three categories of less than three per week, between three per week and three per day, and more than three per day (Table 2). This showed that at least 95 percent of all cases and controls had between three bowel actions per week and three per day (Table 2). Among the small residual group of respondents who fell outside what may be considered as the "normal" number of bowel actions, there were more patients than controls who had less than three

TABLE 1. *Self-reported Constipation, Diarrhea, and Laxative Use*

	Status	Total No. of Respondents in Category	Number With Positive Reply (%)	RR*	95% CI†	P-value
Self-reported constipation	Cases	685	215 (31)	1.27	1.01–1.61	0.05
	Controls	723	191 (26)			
Self-reported constipation in males	Cases	374	97 (26)	1.47	1.05–2.07	0.03
	Controls	396	76 (19)			
Self-reported constipation in females	Cases	311	118 (38)	1.13	0.82–1.56	0.52 NS
	Controls	327	115 (35)			
Constipation in those younger than 65 years	Cases	324	89 (27)	1.53	1.07–2.20	0.03
	Controls	343	68 (20)			
Constipation in those 65 years or older	Cases	361	126 (35)	1.12	0.83–1.52	0.51 NS
	Controls	380	126 (32)			
Constipation in colon cancers	Cases	375	126 (34)	1.41	1.08–1.85	0.02
	Controls	723	191 (26)			
Constipation in rectal cancers	Cases	310	89 (29)	1.12	0.83–1.51	0.49 NS
	Controls	723	191 (26)			
Self-reported diarrhea	Cases	685	29 (4)	1.14	0.67–1.95	0.7 NS
	Controls	723	27 (4)			
Self-reported commercial laxative use	Cases	685	164 (24)	1.10	0.86–1.42	0.5 NS
	Controls	723	160 (22)			

*RR: relative risk.
†95% CI: 95% confidence interval.

bowel actions per week and also more patients than controls who had more than three bowel actions per day (Table 2). This difference was not statistically significant for those having less than three bowel actions per week, but it was statistically significant for those having more than three bowel actions per day for both the previous ten and 20 years. It is emphasized that the total numbers in the subsets reporting more than three bowel actions per day were extremely small (12 patients and two controls for the previous ten years and ten patients and two controls for the previous 20 years). Self-reported consistency of bowel actions examined for the previous ten and 20 years showed no statistically significant differences between patients and controls (Table 3).

Constipation and Diet: A detailed examination was made of the association between self-reported constipation and previous diet. Several dietary factors already found to be statistically significantly associated with the risk of colorectal cancer in this study, which have been reported in detail elsewhere,[12] were examined as potential confounding factors with self-reported constipation. These dietary factors were fiber/vegetable intake, cruciferous vegetable intake, dietary vitamin C intake, beef intake, fat intake, and milk intake (Table 4). This analysis showed that the risk of colorectal cancer is predominantly described by fiber/vegetable intake and cruciferous vegetable intake and not by constipation (Table 4). Table 4 also shows that dietary vitamin C, beef, and milk intake

TABLE 2. *Self-reported Frequency of Bowel Actions*

Years Examined	Usual Number of Bowel Actions	Cases (%)	Controls (%)	Statistical Significance RR*	95% CI†	P-value
Previous 10 years (Total number who had stable bowel habit: 549 cases and 609 controls)	Less than 3 per week	9 (1.6)	4 (0.7)	2.49	0.7–8.5	0.13
	Between 3 per week and 3 per day	528 (96)	603 (99)	1.0	–	–
	More than 3 per day	12 (2.2)	2 (0.3)	6.7	1.5–30.9	0.01
Previous 20 years (Total number who had stable bowel habit: 504 cases and 564 controls)	Less than 3 per week	7 (1.4)	3 (0.5)	2.59	0.6–10.5	0.17
	Between 3 per week and 3 per day	487 (97)	559 (99)	1.0	–	–
	More than 3 per day	10 (2.0)	2 (0.4)	5.39	1.1–25.6	0.03

*RR: relative risk.
†95% CI: 95% confidence interval.

TABLE 3. *Self-reported Consistency of Bowel Actions*

Years Examined	Consistency of Bowel Actions	Cases (%)	Controls (%)	RR*	95% CI†	P-value
Previous 10 years	Liquid/does not					
(Total number who had stable	hold shape	116 (22)	133 (22)	0.97	0.7-1.3	0.8
consistency of bowel actions:	Holds shape	410 (77)	459 (77)	1.0	–	–
535 cases and 597 controls)	Small hard pellets	9 (1.6)	5 (0.8)	2.40	0.7-7.7	0.13
Previous 20 years	Liquid/does not					
(Total number who had stable	hold shape	96 (20)	118 (21)	0.90	0.7-1.2	0.5
consistency of bowel actions:	Holds shape	385 (79)	431 (78)	1.0	–	–
487 cases and 553 controls)	Small, hard pellets	6 (1.2)	4 (0.7)	2.47	0.6-10.4	0.23

*RR: relative risk.
†95% CI: 95% confidence interval.

risks are independent of the constipation risk.

Examination of the fat intake factor with constipation was investigated in more detail by dividing the respondents into a low fat intake group (less than 100 gm per day) and high fat intake group (more than 100 gm per day). This analysis showed that there was a statistically significant positive interaction ($P = .002$) between constipation and high fat intake, that is, the relative risk for those who reported constipation and had a high fat intake was higher than would be expected by the simple multiplicative effect of the two factors acting independently (Table 5).

In the dietary part of the Melbourne study, a model of dietary risk factors that were significantly associated with colorectal cancer risk[12] ($\chi^2_{11} = 212$, $P < .001$) was created. The risk factors in this model were: low intakes of dietary fiber/vegetables, cruciferous vegetables, dietary vitamin C, pork, fish, "other meats" (as defined in the study), vitamin supplements, low *or* high intake of milk drinks and high intakes of fat and, for males only, high intake of beer. Relative risks for those reporting constipation, when estimated by simultaneous adjustment for these dietary variables grouped together as a diet model, showed that the risk of constipation was confounded by the diet model and that the risk of colorectal cancer was predominantly described by that diet model rather than

by self-reported constipation ($\chi^2_1 = 1$, $RR = 1.18$, $P = .3$, CI = .91 to 1.54).

Discussion

There is relatively little data on what constitutes a "normal" number of bowel motions. A study by Connell and co-workers in 1965[10] in which enquiries were made about bowel habits of almost 1500 people who were either not seeking medical advice or did not have known gastrointestinal disease showed that, in 99 percent, the frequency of bowel habit fell between three bowel actions per week and three per day. A more recent study from Australia,[11] which examined the bowel habits of over 200 adults, also showed that about 95 percent of their respondents fell into this category. In the present study also, at least 96 percent of patients and 99 percent of the controls had between three bowel motions per week and three per day (Table 2).

The investigators had several methodologic difficulties with the interpretation of self-reported constipation, probably because the word "constipation" is interpreted in various ways by respondents despite the precise wording of the question in this study. This is reflected by 36 respondents (16 patients and 20 controls) who reported no constipation yet took laxatives in order to make their bowels move. Also, a further 52 respondents (27 patients

TABLE 4. *Statistical Significance of Constipation in Colorectal Cancer after Adjustment for Various Dietary Variables*

Intake of Dietary Factor Which was Adjusted for	X^2_1	P-value	Relative Risk of Constipation	95% CI*	X^2_1 Interaction Between Constipation and Diet
Fiber vegetable	2	0.2	1.22	0.95-1.57	2
Cruciferous vegetable	3	0.08	1.25	0.98-1.60	1
Dietary vitamin C	5†	0.03	1.29	1.01-1.65	0
Beef	5*	0.03	1.28	1.01-1.63	1
Milk drinks	4*	0.05	1.27	0.99-1.62	2
Fat	4*	0.05	1.29	1.02-1.65	5†
Total diet model[12]	1	0.3	1.18	0.91-1.54	–

*95% CI = 95% confidence interval.
†.01 < P < .05.

and 25 controls) reported no constipation, took no laxatives, yet reported the presence of "hard motions." In another study of apparently healthy people,[10] 4 percent reported constipation that, in some, correlated with infrequent bowel actions, in others with hardness of the stool, and often bore no relation to bowel frequency or stool consistency. A further difficulty in this study was the possible confounding of constipation as a presenting symptom of colorectal cancer. To overcome the problem of patients whose presenting symptom was constipation, the question was changed to determine how far back the symptoms went in time, that is, did the constipation appear before the development of their colorectal cancer. This question could not be resolved in some cases, and these were excluded from the analysis as self-reported constipation responses.

There have been six previous case control studies of colorectal cancer in which bowel habit was investigated. Three early studies in the 1960s found no differences in the frequency and severity of constipation, nor in the lifetime patterns of bowel movements.[13-15] In one of these studies,[14] further analysis by subsites of the large bowel also did not show any statistically significant association between the location of the colorectal cancer and the degree of constipation. Three more recent case control studies that, inter alia, studied bowel habit in colorectal cancer[16-18] have had inconsistent findings. One found no statistically significant case control differences in bowel habit,[17] one found that severe long-standing constipation was present statistically significantly more often in patients than in controls and that this difference applied to both colon cancer and rectal cancer cases,[18] and the third study found a highly statistically significant difference in bowel habit in that patients reported diarrhea more frequently than controls.[16] None of these previous case control studies made adjustments for diet as a confounding factor. More than three daily bowel actions were reported statistically significantly more often in patients than in controls in the present study, but as these findings involved only ten cases and two controls for the previous 20 years, no firm conclusions can be drawn. Apart from this finding the frequency and consistency of bowel motions were not associated with the risk of colorectal cancer in this study.

The frequency of regular laxative use in apparently well populations appears to be about 20 percent, having been found in 20 percent of the series of Connell and co-workers,[10] 17 percent in the series of Dent and co-workers,[11] 19 percent in the series of Wu and co-workers,[19] and in 22 percent of the controls in the present study. Also, no statistically significant differences were found in any of the previous case control or cohort studies with respect to laxative use and colorectal cancer risk.[14,16,19,20] The Melbourne study also found no statistically signifi-

TABLE 5. *Examination of Interactions in Risk of Colorectal Cancer With Fat Intake and Constipation*

	Relative Risk* (95% CI)	
	No Constipation Reported	Constipation Reported
Low fat intake (less than 100g fat/day)	1.00	0.85 (0.57–1.26) $P = .4$
High fat intake (more than 100g fat/day)	1.24 (0.89–1.72) $P = .2$	1.88† (1.26–2.80) $P = .002$

*Relative risk estimated by simultaneous adjustment for the dietary model variables described in text. 95% CI = 95% confidence interval.
†$.001 < P < .01$.

cant difference in the distribution of laxative use among patients and controls. Based on currently available evidence, it appears most unlikely that laxative use is associated with colorectal cancer risk.

In this study, dietary habits were found to have an important confounding effect on constipation. A low intake of fiber, vegetables, and vitamin C-containing foods and a high intake of fat were each independently a confounding factor in self-reported constipation (Table 4). Of special interest was the finding that when the constipation risk was simultaneously adjusted for the entire dietary risk model, constipation disappeared as a risk factor in colorectal cancer (Table 4). This means that it is the dietary pattern and not the constipation that is associated with the risk of colorectal cancer. Of further interest in the present study was the finding that high fat intake and chronic constipation are highly statistically significantly associated with the risk of colorectal cancer (Table 5). This finding is consistent with the hypothesis that fat, with slow transit through the large bowel and increased degradation of secondary bile acids by bacteria, is one of the etiologic factors in the neoplastic transformation of the large-bowel epithelium.[3,21]

The authors conclude that chronic constipation is a marginal risk factor in colorectal cancer and is therefore of some value as an indicator of risk for screening purposes, but that it is significantly confounded by the dietary pattern of the individual and, in itself, is not an etiologic factor in colorectal cancer. It is also concluded that the frequency and consistency of bowel movements, as well as diarrhea and laxative use, are unlikely to be etiologic factors, nor are they likely to be associated with the risk of colorectal cancer.

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