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Original Contribution

Bowel Movement and Constipation Frequencies and the Risk of Colorectal Cancer Among Men in the Netherlands Cohort Study on Diet and Cancer

Colinda C. J. M. Simons*, Leo J. Schouten, Matty P. Weijenberg, R. Alexandra Goldbohm, and Piet A. van den Brandt

* Correspondence to Colinda Simons, Department of Epidemiology, Faculty of Health, Medicine and Life Sciences, Maastricht University, P.O. Box 616, 6200 MD Maastricht, the Netherlands (e-mail: colinda.simons@epid.unimaas.nl).

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The authors investigated the associations between bowel movement and constipation frequencies and colorectal cancer (CRC) endpoints among men in the Netherlands Cohort Study on Diet and Cancer ($n = 58{,}279$) and explored whether dietary fiber intake may modify associations. After 13.3 years (1986–1999), 1,207 CRC cases and 1,753 subcohort members were available for case-cohort analyses. Multivariate analyses showed a significantly increased hazard ratio for CRC overall and rectal cancer in men who reported having a bowel movement 1–2 times per day (second-highest category) as compared with once a day (CRC: hazard ratio (HR) = 1.29, 95% confidence interval (CI): 1.09, 1.53 ($P_{trend} < 0.001$); rectal cancer: HR = 1.50, 95% CI: 1.15, 1.95 ($P_{trend} = 0.001$)). Hazard ratios for CRC overall and rectal cancer were significantly decreased and lowest in men who reported suffering from constipation sometimes or more often versus never (CRC: HR = 0.76, 95% CI: 0.58, 0.98 ($P_{trend} = 0.02$); rectal cancer: HR = 0.57, 95% CI: 0.35, 0.90 ($P_{trend} = 0.01$)). No trends in the associations with proximal or distal colon cancer risk were observed. Interactions with dietary fiber intake were not significant. In this study, frequent bowel movements were associated with an increased risk of rectal cancer in men, and constipation was associated with a decreased risk.

cohort studies; colonic neoplasms; constipation; defecation; rectal neoplasms

Abbreviations: CI, confidence interval; FFQ, food frequency questionnaire; HR, hazard ratio; ICDO-1, *International Classification of Diseases for Oncology*, First Edition; NLCS, Netherlands Cohort Study on Diet and Cancer.

Gut motility may be one of the mechanisms linking dietary factors and physical activity with colorectal cancer risk. A hypothesis by Burkitt et al. (1) predicts that decreased gut motility may increase colorectal cancer risk because carcinogens in stool are held in contact with the colonic mucosa for a longer duration of time and the concentration of carcinogens in the colon may increase. Decreased gut motility may be the result of low fiber intake, low fluid intake, and low levels of physical activity (2).

Previously, most studies have not investigated measurable aspects of gut motility such as bowel movement and constipation frequencies. Instead, researchers have focused on fiber intake, mentioning gut motility as a possible explanation for the protective effect of fiber found in some studies (3). Those studies that have been conducted have yielded inconsistent results. A meta-analysis of case-control studies conducted in 1993 (4) and several later case-control studies (5–9) associated infrequent bowel movements or constipation with an increased risk of colorectal cancer. Prospective cohort studies and a nested case-control study associated infrequent bowel movements with increased colorectal cancer risk (10, 11), showed no association between bowel movement frequency and colorectal cancer risk (12–14), or even suggested that frequent bowel movements may enhance risk (10).

When investigating the association between bowel movement and constipation frequencies and colorectal cancer risk, prospective studies with long follow-up periods may be preferred over those with short follow-up periods or case-control studies, because reverse causation is less likely to be

in play. This is important, because changes in bowel habits and constipation can be symptoms of colorectal cancer (15). Additionally, prospective studies are less prone to selection and information bias. The prospective studies conducted thus far (10–14) have been limited by the fact that only 3 examined colon and rectal cancer risk separately (11–13), while associations may differ by subsite. Depending on whether the rectum acts as a storage organ or a conduit organ—both of which are argued as possible (16–18)—the rectum as compared with the colon may be more or less affected by carcinogens in stool, and cancer risks may differ. Therefore, it is worthwhile investigating the associations between bowel movement and constipation frequencies and colorectal cancer risk, overall and at subsites. Additionally, it may be worthwhile analyzing possible effect modification by dietary fiber intake, because fiber intake may decrease colorectal cancer risk not only by increasing bowel movement frequency (provided that sufficient fluid is available (2)) but also by diluting carcinogens and binding carcinogenic bile acids, thereby producing short-chain fatty acids, which have been suggested to promote anticarcinogenic action (19).

Within the Netherlands Cohort Study on Diet and Cancer (NLCS), which includes 120,852 men and women, information on bowel movement and constipation frequencies is available for men only. This enabled us to investigate the associations between bowel movement and constipation frequencies and colorectal cancer risk overall and at subsites in men. We also explored whether dietary fiber intake may modify these associations.

MATERIALS AND METHODS

Study population and design

The NLCS has been described in detail elsewhere (20). Briefly, the NLCS includes 58,279 men who were aged 55–69 years at baseline in 1986 when they completed a mailed self-administered questionnaire on diet and cancer. Bowel movement and constipation frequencies were addressed in the questionnaire for men only, by means of the multiple-choice questions ''How often do you usually have a bowel movement?'' and ''Do you ever suffer from constipation?''. The questionnaire for women did not include these questions because of limited space, due to the inclusion of questions related to hormonal factors. The baseline questionnaire included a 150-item semiquantitative food frequency questionnaire (FFQ). Dietary fiber intake and other nutrient intakes were calculated from the FFQ using the Dutch food composition table for 1986–1987 (21). With respect to fiber supplements, our measure of dietary fiber intake included fiber from bran and wheat germs. The FFQ was validated against a 9-day dietary record and was found to rank participants adequately according to intake of the food groups and nutrients investigated. The Pearson correlation coefficient for the correlation between dietary fiber intake as assessed by the questionnaire and intake as estimated from the 9-day diet record was 0.74 (22). In a reproducibility study, the FFQ was shown to be a good indicator of nutrient intake over a period of at least 5 years. The Pearson correlation coefficient for the correlation between paired measurements of dietary fiber intake assessed by the FFQ was 0.68 for men (23).

We used a case-cohort approach for data processing and analysis for reasons of efficiency, enumerating cases for the entire cohort and calculating the person-time at risk from a random subcohort of 5,000 members—of whom 2,411 were men—who were followed up for vital status. Incident cases of colorectal cancer were ascertained through the Netherlands population-based cancer registry and the Netherlands nationwide pathology registry (24, 25). The estimated completeness of cancer follow-up was more than 96% (26). Excluded from analyses were men who reported a history of cancer other than nonmelanoma skin cancer at baseline, men with an inconsistent/incomplete baseline dietary questionnaire, and men with missing information on bowel movement and constipation frequencies and potential confounders. After 13.3 years of follow-up, these criteria left 1,753 male subcohort members and 1,207 male colorectal cancer cases available for analysis. Among the 1,207 male colorectal cancer cases, there were 345 cases of proximal colon cancer (*International Classification of Diseases for Oncology*, First Edition (ICDO-1), codes 153.0, 153.1, 153.4, 153.5, and 153.6), 401 cases of distal colon cancer (ICDO-1 codes 153.2, 153.3, and 153.7), and 308 cases of rectal cancer (ICDO-1 code 154.1). The remaining cases were cases of rectosigmoid cancer (ICDO-1 code 154.0) or colon cancer (ICDO-1 codes 153.8 and 153.9) that could not be classified as either proximal or distal and were included only when analyzing overall colorectal cancer risk.

The NLCS has been approved by the institutional review boards of the TNO Nutrition and Food Research Institute (Zeist, the Netherlands) and Maastricht University (Maastricht, the Netherlands).

Statistical analysis

Hazard ratios and corresponding 95% confidence intervals for colorectal cancer endpoints were estimated across categories of bowel movement and constipation frequencies using the Cox proportional hazards model with Stata software (Stata Corporation, College Station, Texas). For bowel movement frequency, possible answers were ''more than 2 times per day,'' ''1–2 times per day,'' ''once a day,'' ''every 2 days,'' and ''2 times per week or less.'' The categories ''every 2 days'' and ''2 times per week or less'' were combined into the category ''every 2 days or less'' because of limited numbers. For constipation frequency, possible answers were ''never,'' ''seldom,'' ''sometimes,'' ''often,'' and ''very often.'' The categories ''sometimes,'' ''often,'' and ''very often'' were combined into the category ''sometimes or more often'' because of limited numbers. In accordance with the literature, reference categories were chosen as ''once a day'' for bowel movement frequency and ''never'' for constipation frequency. Standard errors were estimated using the robust Huber-White sandwich estimator to account for the additional variance introduced by sampling the subcohort from the entire cohort (27). The proportional hazards assumption was tested using the scaled Schoenfeld residuals (28). If this assumption seemed to be violated, hazard curves

Table 1. Bowel Movement and Constipation Frequencies and Distributions of Potential Confounders in Male Subcohort Members and Colorectal Cancer Cases, Netherlands Cohort Study on Diet and Cancer, 1986–1999

Characteristic	Subcohort (n = 1,753)		Colorectal Cancer Cases (n = 1,207)		Colorectal Cancer Subsite					
					Proximal Colon (n = 345)		Distal Colon (n = 401)		Rectum (n = 308)	
	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)
Bowel movement frequency										
>2 times per day	3.4		4.1		3.8		2.7		3.9	
1–2 times per day	34.2		39.0		33.3		39.4		43.5	
Once a day	54.9		52.0		56.2		51.9		48.7	
Every 2 days or less	7.5		5.0		6.7		6.0		3.9	
Constipation frequency										
Never	53.3		56.5		52.8		51.9		62.7	
Seldom	34.6		33.6		37.7		35.2		29.6	
Sometimes or more often	12.1		9.9		9.6		13.0		7.8	
Age, years		61.2 (4.2)		62.1 (4.1)		62.4 (4.0)		62.1 (4.2)		61.5 (3.9)
Family history of colorectal cancer (yes)	5.5		10.1		11.0		10.0		8.8	
Occupational physical activity (calculated for the longest-held job), kJ/minute										
<8	59.3		64.5		65.5		70.8		54.6	
8–12	25.5		22.8		23.2		17.7		28.9	
>12	15.2		12.7		11.3		11.5		16.6	
Nonoccupational physical activity, minutes/day										
≤30	17.3		15.1		15.4		14.5		14.6	
>30–60	31.7		32.2		35.7		29.7		29.9	
>60–90	18.6		20.3		16.2		23.2		22.4	
>90	32.4		32.4		32.8		32.7		33.1	
Smoking status										
Never smoker	13.0		10.6		10.7		11.2		9.7	
Ex-smoker	52.7		60.6		58.6		65.1		56.5	
Current smoker	34.4		28.8		30.7		23.7		33.8	
Alcohol intake, g/day										
0	14.4		12.0		13.0		13.2		11.0	
0.1–29	70.1		69.9		73.6		68.1		67.2	
≥30	15.5		18.1		13.3		18.7		21.8	
Socioeconomic status (by educational level)										
Primary school	22.2		22.0		22.6		17.2		26.3	
Lower vocational	20.4		19.6		15.7		18.0		26.0	
Junior high school	36.7		37.6		43.5		37.2		31.2	
Higher vocational/university	20.7		20.8		18.3		27.7		16.6	
Body mass index[a]		24.9 (2.5)		25.2 (2.6)		25.2 (2.7)		25.4 (2.7)		25.0 (2.6)
Fresh meat intake, g/day		106 (42.5)		104 (40.4)		102 (39.7)		105 (40.2)		105 (42.1)
Processed meat intake, g/day		17.0 (17.2)		17.9 (17.7)		18.4 (19.3)		17.7 (15.9)		17.4 (16.9)
Dietary fiber intake, g/day		28.7 (8.6)		28.4 (8.2)		27.9 (8.2)		28.3 (7.9)		29.4 (8.6)

Abbreviation: SD, standard deviation.
[a] Weight (kg)/height $(m)^2$.

Table 2. Cross-Tabulation of Male Subcohort Members ($n = 1,753$) by Category of Bowel Movement and Constipation Frequencies, Netherlands Cohort Study on Diet and Cancer, 1986–1999*

Constipation Frequency	Bowel Movement Frequency							
	>2 Times per Day		1–2 Times per Day		Once a Day		Every 2 Days or Less	
	No.	%	No.	%	No.	%	No.	%
Never	32	54.2	359	59.8	511	53.1	32	24.4
Seldom	20	33.9	199	33.2	350	36.3	38	29.0
Sometimes or more often	7	11.9	42	7.0	102	10.6	61	46.6
Total	59		600		963		131	

* $P < 0.001$ (Pearson's χ^2 test for the relation between bowel movement and constipation frequencies).

were inspected visually and analyses were conducted for short and long durations of follow-up by splitting the follow-up time at 7 years (<7 years vs. ≥7 years).

Hazard ratios and 95% confidence intervals were estimated with an age-adjusted model and a multivariate model. In the multivariate model, we adjusted for potential confounders selected a priori from the literature and those that introduced a >10% change in hazard ratios or contributed significantly to the model. A priori selected potential confounders were: family history of colorectal cancer, occupational physical activity (calculated for the longest-held job), nonoccupational physical activity, smoking status, alcohol intake, body mass index (weight (kg)/height $(m)^2$), fresh meat intake, processed meat intake, and dietary fiber intake. Other potential confounders considered were socioeconomic status (defined by educational level), self-reported diabetes, and intakes of total energy, folate, β-carotene, vitamin B_6, vitamin C, vitamin E, fruit, vegetables, dietary water, calcium, total fat (energy-adjusted), magnesium, and heme iron. Of these factors, socioeconomic status (by educational level) contributed significantly to the model and was included. Additionally, hazard ratios were estimated with models mutually adjusted for constipation or bowel movement frequency. Interactions between bowel movement and constipation frequencies, on the one hand, and tertiles of dietary fiber intake based on intake among male subcohort members, on the other hand, were tested using cross-product terms.

In a sensitivity analysis, we checked whether hazard ratios for the association between bowel movement frequency and colorectal cancer risk differed when no adjustment was made for dietary fiber intake, because bowel movement frequency may be an intermediate factor in the association between dietary fiber intake and colorectal cancer risk. We also repeated analyses after excluding participants who reported chronic bowel disorders at baseline. Furthermore, because dietary fiber may bulk feces and increase gut motility only when sufficient fluid is available (2), we created a combination variable for dietary fiber and dietary water intake and investigated interactions once more. Dietary water intake from foods and fluids was calculated using the 1986–1987 Dutch food composition table (21). Categories were "low fiber/low water intake," "high fiber/low water intake," "low fiber/high water intake," and "high fiber/high water intake." Finally, to check for the influence of preclinical disease, we repeated the analyses after excluding the first 2 years of follow-up and for the first 2 years of follow-up only. Statistical significance was indicated by a P value less than 0.05 for 2-sided testing.

RESULTS

Table 1 shows bowel movement and constipation frequencies and data on potential confounders for male subcohort members and colorectal cancer cases. The cross-tabulation of bowel movement and constipation frequencies in Table 2 shows that men who reported having a bowel movement every 2 days or less, as compared with men in other bowel movement categories, were more likely to fall into the highest constipation frequency category.

Multivariate analyses showed significantly increased hazard ratios for colorectal cancer, particularly distal colon cancer and rectal cancer, in men who reported having a bowel movement 1–2 times per day as compared with once a day (hazard ratio (HR) = 1.29 (95% confidence interval (CI): 1.09, 1.53), HR = 1.29 (95% CI: 1.01, 1.64), and HR = 1.50 (95% CI: 1.15, 1.95), respectively). In men who reported having a bowel movement more than 2 times per day, in comparison with once a day, hazard ratios leveled off and were not significant, possibly because of limited statistical power. Hazard ratios across subsites were nonsignificantly decreased in men who reported having a bowel movement every 2 days or less as compared with once a day. Tests for trend showed significant positive associations with the risks of colorectal and rectal cancer ($P_{trend} < 0.001$ and $P_{trend} = 0.001$, respectively) but not the risks of proximal and distal colon cancer (Table 3).

With respect to constipation frequency, a significantly decreased hazard ratio for colorectal cancer was observed in men who reported suffering from constipation sometimes or more often as compared with never (HR = 0.76, 95% CI: 0.58, 0.98). Significantly decreased hazard ratios for rectal cancer were observed in men who reported suffering from constipation seldom and sometimes or more often, as compared with never (HR = 0.75 (95% CI: 0.56, 0.99) and HR = 0.57 (95% CI: 0.35, 0.90), respectively). Tests for trend showed significant inverse associations with colorectal and rectal cancer risk ($P_{trend} = 0.02$ and $P_{trend} = 0.01$, respectively). No associations were observed between constipation frequency and proximal and distal colon cancer risk (Table 3).

Additional mutual adjustment in multivariate analyses yielded comparable results, although hazard ratios were slightly attenuated (Table 3). Furthermore, a sensitivity analysis showed that results were comparable when no adjustment was made for dietary fiber intake. The same was true after excluding participants who reported chronic bowel disorders at baseline ($n = 75$), although hazard ratios for the association between constipation frequency and colorectal and rectal cancer risk were attenuated, and a significant trend in the association with colorectal cancer risk was no longer present (data not shown).

Table 3. Hazard Ratios for Colorectal Cancer Overall and at Subsites in Relation to Bowel Movement and Constipation Frequencies in Men, Netherlands Cohort Study on Diet and Cancer, 1986–1999

Colorectal Cancer Subsite	Bowel Movement Frequency							*P* for Trend	Constipation Frequency					*P* for Trend
	>2 Times per Day (695 PY)		1–2 Times per Day (7,030 PY)		Once a Day (Referent) (11,296 PY)	Every 2 Days or Less (1,492 PY)			Never (Referent) (10,995 PY)	Seldom (7,077 PY)		Sometimes or More Often (2,440 PY)		
	HR	95% CI	HR	95% CI	(HR = 1)	HR	95% CI		(HR = 1)	HR	95% CI	HR	95% CI	
Colorectum														
No. of cases	49		471		627	60			682	405		120		
Age-adjusted HR	1.31	0.88, 1.96	1.26	1.07, 1.48	1	0.71	0.51, 0.98	<0.001	1	0.91	0.77, 1.08	0.77	0.60, 0.99	0.03
Multivariate HR[a]	1.23	0.81, 1.88	1.29	1.09, 1.53	1	0.72	0.52, 1.01	<0.001	1	0.89	0.75, 1.05	0.76	0.58, 0.98	0.02
Multivariate HR[b]	1.22	0.80, 1.87	1.28	1.08, 1.51	1	0.76	0.54, 1.08	0.001	1	0.91	0.77, 1.08	0.83	0.63, 1.09	0.13
Proximal colon														
No. of cases	13		115		194	23			182	130		33		
Age-adjusted HR	1.14	0.60, 2.14	1.00	0.78, 1.30	1	0.87	0.54, 1.39	0.57	1	1.09	0.85, 1.40	0.78	0.52, 1.17	0.54
Multivariate HR[a]	1.08	0.55, 2.11	1.06	0.81, 1.38	1	0.87	0.53, 1.40	0.46	1	1.04	0.80, 1.35	0.75	0.50, 1.13	0.35
Multivariate HR[b]	1.08	0.55, 2.11	1.05	0.81, 1.38	1	0.94	0.57, 1.56	0.61	1	1.05	0.81, 1.36	0.77	0.50, 1.18	0.47
Distal colon														
No. of cases	11		158		208	24			208	141		52		
Age-adjusted HR	0.89	0.46, 1.73	1.27	1.01, 1.61	1	0.85	0.54, 1.36	0.07	1	1.04	0.82, 1.32	1.09	0.78, 1.54	0.59
Multivariate HR[a]	0.80	0.40, 1.60	1.29	1.01, 1.64	1	0.88	0.54, 1.42	0.12	1	0.98	0.77, 1.26	1.05	0.73, 1.50	0.89
Multivariate HR[b]	0.81	0.40, 1.61	1.29	1.01, 1.64	1	0.84	0.50, 1.40	0.10	1	1.01	0.78, 1.29	1.12	0.77, 1.64	0.63
Rectum														
No. of cases	12		134		150	12			193	91		24		
Age-adjusted HR	1.32	0.69, 2.52	1.47	1.14, 1.90	1	0.60	0.32, 1.11	<0.001	1	0.73	0.56, 0.96	0.55	0.35, 0.87	0.002
Multivariate HR[a]	1.25	0.64, 2.42	1.50	1.15, 1.95	1	0.63	0.33, 1.17	0.001	1	0.75	0.56, 0.99	0.57	0.35, 0.90	0.01
Multivariate HR[b]	1.25	0.64, 2.43	1.47	1.13, 1.92	1	0.72	0.38, 1.37	0.002	1	0.77	0.58, 1.02	0.64	0.40, 1.04	0.02

Abbreviations: CI, confidence interval; HR, hazard ratio; PY, person-years.

[a] Adjusted for age, family history of colorectal cancer, occupational physical activity (calculated for the longest-held job), nonoccupational physical activity, smoking status, alcohol intake, socioeconomic status (by educational level), body mass index, fresh meat intake, processed meat intake, and dietary fiber intake.

[b] Additionally mutually adjusted for constipation or bowel movement frequency.

Table 4. Hazard Ratios for Colorectal Cancer Overall in Relation to Bowel Movement and Constipation Frequencies in Men, by Tertile of Dietary Fiber Intake, Netherlands Cohort Study on Diet and Cancer, 1986–1999

Tertile of Dietary Fiber Intake[a]	Bowel Movement Frequency							*P* for Trend	*P* for Interaction	Constipation Frequency					*P* for Trend	*P* for Interaction
	>2 Times per Day		1–2 Times per Day		Once a Day (Referent)	Every 2 Days or Less				Never (Referent)	Seldom		Sometimes or More Often			
	HR	95% CI	HR	95% CI	(HR = 1)	HR	95% CI			(HR = 1)	HR	95% CI	HR	95% CI		
Tertile 1																
Person-years	168		2,263		3,560	513				3,423	2,291		789			
No. of cases	15		163		203	23				223	135		46			
Multivariate HR[b]	1.45	0.58, 3.61	1.33	0.98, 1.82	1	0.80	0.45, 1.45	0.04		1	0.88	0.64, 1.19	0.92	0.58, 1.45	0.50	
Multivariate HR[c]	1.45	0.58, 3.63	1.32	0.96, 1.81	1	0.80	0.44, 1.48	0.04		1	0.91	0.66, 1.25	1.00	0.62, 1.61	0.76	
Tertile 2																
Person-years	222		2,265		3,890	603				3,500	2,649		829			
No. of cases	19		143		209	20				205	148		38			
Multivariate HR[b]	1.60	0.78, 3.28	1.20	0.88, 1.64	1	0.55	0.31, 0.98	0.01		1	0.97	0.72, 1.30	0.70	0.44, 1.13	0.22	
Multivariate HR[c]	1.63	0.79, 3.36	1.20	0.88, 1.63	1	0.59	0.32, 1.10	0.01		1	1.00	0.74, 1.35	0.83	0.50, 1.39	0.61	
Tertile 3																
Person-years	306		2,503		3,846	375				4,072	2,137		822			
No. of cases	15		165		215	17				254	122		36			
Multivariate HR[b]	0.92	0.45, 1.87	1.26	0.94, 1.69	1	0.87	0.44, 1.71	0.23	0.80	1	0.92	0.68, 1.25	0.64	0.39, 1.03	0.09	0.79
Multivariate HR[c]	0.90	0.44, 1.83	1.24	0.93, 1.67	1	0.99	0.49, 2.00	0.36	0.81	1	0.92	0.68, 1.25	0.65	0.39, 1.08	0.12	0.80

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] The ranges of dietary fiber intake in tertiles 1, 2, and 3 were approximately 5.8–24.2 g/day, 24.3–31.3 g/day, and 31.4–73.9 g/day, respectively.

[b] Adjusted for age, family history of colorectal cancer, occupational physical activity (calculated for the longest-held job), nonoccupational physical activity, smoking status, alcohol intake, socioeconomic status (by educational level), body mass index, fresh meat intake, processed meat intake, and dietary fiber intake.

[c] Additionally mutually adjusted for constipation or bowel movement frequency.

Table 5. Hazard Ratios for Colorectal Cancer Overall and at Subsites in Relation to Bowel Movement and Constipation Frequencies in Men, for Short (<7 Years) and Long (≥7 Years) Durations of Follow-Up, Netherlands Cohort Study on Diet and Cancer, 1986–1999

Colorectal Cancer Subsite and Duration of FU	Bowel Movement Frequency							*P* for Trend	Constipation Frequency					*P* for Trend
	>2 Times per Day		1-2 Times per Day		Once a Day (Referent)	Every 2 Days or Less			Never (Referent)	Seldom		Sometimes or More Often		
	HR	95% CI	HR	95% CI	(HR = 1)	HR	95% CI		(HR = 1)	HR	95% CI	HR	95% CI	
Person-years														
<7 years of FU		396		3,995	6,385		865		6,209		4,033		1,400	
≥7 years of FU		299		3,035	4,911		627		4,786		3,044		1,041	
Colorectum														
<7 years of FU														
No. of cases		27		199	258		29		289		177		47	
Multivariate HR[a]	1.59	0.97, 2.62	1.32	1.06, 1.65	1	0.79	0.51, 1.24	0.001	1	0.88	0.70, 1.10	0.65	0.46, 0.94	0.02
Multivariate HR[b]	1.57	0.95, 2.60	1.30	1.05, 1.63	1	0.89	0.56, 1.42	0.01	1	0.90	0.72, 1.13	0.71	0.48, 1.03	0.07
≥7 years of FU														
No. of cases		22		272	369		31		393		228		73	
Multivariate HR[a]	0.96	0.56, 1.65	1.26	1.03, 1.54	1	0.66	0.44, 1.01	0.01	1	0.89	0.72, 1.09	0.83	0.61, 1.13	0.15
Multivariate HR[b]	0.96	0.56, 1.64	1.26	1.03, 1.54	1	0.68	0.44, 1.05	0.01	1	0.91	0.74, 1.12	0.93	0.68, 1.28	0.44
Proximal colon														
<7 years of FU														
No. of cases		9		43	83		13		76		58		14	
Multivariate HR[a]	1.76	0.80, 3.89	0.93	0.62, 1.38	1	1.11	0.59, 2.09	0.77	1	1.09	0.75, 1.57	0.72	0.40, 1.33	0.53
Multivariate HR[b]	1.78	0.81, 3.92	0.92	0.62, 1.37	1	1.26	0.64, 2.48	0.91	1	1.09	0.75, 1.58	0.68	0.36, 1.30	0.49
≥7 years of FU														
No. of cases		4		72	111		10		106		72		19	
Multivariate HR[a]	0.57	0.19, 1.70	1.14	0.82, 1.59	1	0.68	0.34, 1.33	0.44	1	1.01	0.72, 1.40	0.78	0.46, 1.32	0.48
Multivariate HR[b]	0.57	0.19, 1.71	1.14	0.82, 1.59	1	0.71	0.35, 1.43	0.55	1	1.03	0.73, 1.44	0.85	0.49, 1.46	0.73
Distal colon														
<7 years of FU														
No. of cases		5		66	78		10		85		54		20	
Multivariate HR[a]	0.91	0.35, 2.38	1.42	1.00, 2.03	1	0.90	0.43, 1.86	0.12	1	0.90	0.62, 1.30	0.93	0.54, 1.60	0.65
Multivariate HR[b]	0.91	0.35, 2.36	1.42	0.99, 2.03	1	0.89	0.41, 1.95	0.13	1	0.92	0.64, 1.34	1.00	0.56, 1.81	0.85
≥7 years of FU														
No. of cases		6		92	130		14		123		87		32	
Multivariate HR[a]	0.73	0.30, 1.78	1.21	0.89, 1.63	1	0.87	0.47, 1.59	0.38	1	1.04	0.76, 1.41	1.12	0.73, 1.74	0.61
Multivariate HR[b]	0.74	0.30, 1.80	1.22	0.90, 1.64	1	0.82	0.44, 1.53	0.31	1	1.06	0.78, 1.44	1.20	0.76, 1.88	0.44
Rectum														
<7 years of FU														
No. of cases		5		60	67		6		83		46		9	

Multivariate HR[a]	1.15	0.44, 3.01	1.50	1.03, 2.17	1	0.66	0.28, 1.57	0.02	1	0.83	0.56, 1.23	0.47	0.23, 0.97	0.04
Multivariate HR[b]	1.15	0.44, 3.03	1.47	1.01, 2.14	1	0.80	0.34, 1.90	0.05	1	0.86	0.58, 1.27	0.52	0.25, 1.07	0.09
≥7 years of FU														
No. of cases		7		74	83		6		110		45		15	
Multivariate HR[a]	1.34	0.57, 3.12	1.49	1.05, 2.11	1	0.60	0.25, 1.42	0.01	1	0.68	0.47, 0.98	0.65	0.36, 1.17	0.04
Multivariate HR[b]	1.34	0.57, 3.13	1.47	1.04, 2.08	1	0.66	0.27, 1.63	0.01	1	0.70	0.48, 1.02	0.75	0.41, 1.37	0.10

Abbreviations: CI, confidence interval; FU, follow-up; HR, hazard ratio.

[a] Adjusted for age, family history of colorectal cancer, occupational physical activity (calculated for the longest-held job), nonoccupational physical activity, smoking status, alcohol intake, socioeconomic status (by educational level), body mass index, fresh meat intake, processed meat intake, and dietary fiber intake.

[b] Additionally mutually adjusted for constipation or bowel movement frequency.

Table 4 shows the results for the associations between bowel movement and constipation frequencies and colorectal cancer risk, within tertiles of dietary fiber intake. Associations were not evidently dependent on dietary fiber intake, and interactions between bowel movement and constipation frequencies on the one hand and dietary fiber intake on the other hand were not significant. Results for subsite analyses were similar (data not shown). Again, additional mutual adjustment yielded comparable results. When interactions were tested using a combination variable for dietary fiber and water intake, no significant results emerged (data not shown).

Table 5 shows the results of analyses for short and long durations of follow-up after splitting the follow-up time at 7 years. Comparable estimates emerged, although, for long follow-up (≥7 years), hazard ratios for the association between constipation frequency and colorectal cancer risk were attenuated and a significant trend was no longer present. Analyses excluding the first 2 years of follow-up yielded estimates comparable with our main results (data not shown). Analyses for the first 2 years of follow-up showed significantly increased hazard ratios for colorectal cancer in men who reported having bowel movements 1–2 times per day and more than 2 times per day, as compared with once a day. Tests for trend showed significant positive associations with colorectal and rectal cancer risk. We observed no associations between constipation frequency and colorectal cancer endpoints. However, the number of cases after 2 years of follow-up was low, yielding unstable estimates (data not shown).

DISCUSSION

In this study, a significantly increased risk of colorectal cancer, particularly distal colon cancer and rectal cancer, was observed in men who reported having a bowel movement 1–2 times per day as compared with once a day, but not in other categories. Colorectal and rectal cancer risks were significantly decreased in men who reported having constipation to some extent as compared with none. Tests for trend were significant for associations with colorectal and rectal cancer risk, indicating positive associations for bowel movement frequency and inverse associations for constipation frequency. No significant trends were observed in the associations with proximal and distal colon cancer risk. There was no evidence of effect modification by dietary fiber intake. In a pooled analysis of prospective studies, including the NLCS, Park et al. (19) found dietary fiber intake to be inversely associated with colorectal cancer risk in age-adjusted analyses.

Our findings do not confirm the hypothesis of Burkitt et al. (1) and are in contrast with a 1993 meta-analysis of case-control studies (4) and several later case-control studies that associated infrequent bowel movements or constipation with an increased risk of colorectal cancer or colon cancer (5–9). Of the prospective studies conducted, one found an increased risk of colorectal cancer, particularly colon cancer, in persons having infrequent bowel movements (i.e., less than daily) (11), and another found an increased colorectal cancer risk in persons having highly

infrequent bowel movements (i.e., every 6 days or less) (10). The latter study suggested that highly frequent bowel movements may also enhance risk (10), which is consistent with our study. In 2 other prospective studies (12, 13) and 1 case-control study nested within the European Investigation into Cancer and Nutrition–Norfolk (14), investigators concluded that there was no association. However, a significantly increased colorectal cancer risk for frequent bowel movements (i.e., $\geq$2–3 per day) was observed in the nested case-control study (14) when adjusting for lifestyle factors only, instead of lifestyle factors and laxative use.

Attenuation after adjustment for laxative use may have occurred in the nested case-control study (14) because laxative use may predict bowel movement frequency. Alternatively, attenuation might mean that laxative use is the explanatory factor behind the increased risk, as laxative use increases bowel movement frequency and specific laxatives have been indicated to be colorectal cancer risk factors (29–33). However, not all studies have shown support for this (31, 34–36), and some have even suggested antitumoral effects (37, 38). In studies on bowel movement and constipation frequencies, overall laxative use was not consistently associated with colorectal cancer risk (4, 8–12, 14). We could not check whether adjustment for laxative use attenuated our results because insufficient baseline information was available on laxative use. Only 18 male subcohort members (1.0%) reported laxative use in reply to the question ''What medicine(s) have you used for longer than 6 months?'', making underreporting likely. However, laxative use among men in the Netherlands may have been low, as the percentage of laxative users among men aged 45 years or older between 2000 and 2009 was 3.2% or less (39).

A different explanation for the increased (colo)rectal cancer risk observed for frequent bowel movements may involve prostaglandin E_2. Besides its role in inflammation (40), prostaglandin E_2 is thought to promote tumor growth by enhancing cell proliferation, promoting angiogenesis, and inhibiting apoptosis (41–44). Prostaglandin E_2 has also been reported to mediate peristalsis in animal studies, although findings mainly concerned effects in the small intestine (42). To check the plausibility that the effects of prostaglandin E_2 (partly) underlie the increased risk found, we performed 4 extra analyses. In these analyses, we additionally adjusted for linoleic acid intake, linolenic acid intake, total polyunsaturated fatty acid intake, and intake of aspirin and other nonsteroidal antiinflammatory drugs. The rationale for this was that linoleic acid and linolenic acid can be converted into arachidonic acid, which is converted into prostaglandin H_2 (a precursor of prostaglandin E_2) by the activity of cyclooxygenases 1 and 2 (45). Nonsteroidal antiinflammatory drugs are known to inhibit the activity of cyclooxygenases 1 and 2 (41, 43), thereby reducing prostaglandin E_2 levels (45). Furthermore, derivatives of polyunsaturated fatty acids other than arachidonic acid compete with arachidonic acid for enzymes that convert arachidonic acid into prostaglandins (40). No essentially different results emerged from these analyses (data not shown), providing no indication that the effects of prostaglandin E_2 (partly) underlie the increased (colo)rectal cancer risk for frequent bowel movements.

To our knowledge, the finding of a significantly decreased (colo)rectal cancer risk for constipation has not been reported before. Because constipation can be a symptom of colorectal cancer (15), results should be interpreted with caution. Following the hypothesis that cancer risk may increase if carcinogens in stool are in contact with the mucosa for an extended duration of time, the finding of a decreased rectal cancer risk suggests that the rectum predominantly acts as a conduit organ and that stool is stored more proximally in the colorectal tract when a person is constipated. However, one would then expect an increased cancer risk in the distal colon or rectosigmoid junction. We did not observe an increased distal colon cancer risk, but we could not investigate the association with rectosigmoid cancer risk because of limited power. We must also note that the results for constipation were not robust in several sensitivity analyses and that people may define constipation differently according to their usual bowel movement frequency. The cross-tabulation of bowel movement and constipation frequencies and the comparable results obtained from mutually adjusted models indicate that these frequencies did not measure the exact same exposure.

Strengths of this study include the prospective design and the high completeness of follow-up (>96% (26)), making it unlikely that selection or information bias influenced our results. Furthermore, the large number of participants and the measurement of many risk factors at baseline enabled us to perform analyses for colorectal cancer subsites and to adjust for potential confounders. However, in the stratified analyses, case numbers within tertiles of fiber intake were low for some categories.

A possible limitation may be that data on bowel movement and constipation frequencies were self-reported and were not validated or tested for reproducibility. Therefore, misclassification cannot be ruled out, and it may be questioned whether a single measurement at baseline was representative of a period of 13.3 years. If potential misclassification was independent of disease, attenuation of the estimates will most likely have resulted. When the baseline measurement was not representative over 13.3 years, it may have been that bowel movement frequency decreased and constipation frequency increased, since age is thought to be correlated with a decrease in gut motility, either directly or because of the intake of constipating drugs, reduced dietary fiber intake, and lower levels of physical activity (46, 47). Interestingly, an extra analysis showed frequent bowel movements to be associated with an increased risk of colorectal cancer, particularly distal colon and rectal cancer, and constipation to be associated with a decreased risk of rectal cancer in men older than age 61 years but not in men aged 61 years or younger (data not shown). Limitations of our dietary fiber intake measure may be that fiber intake was overestimated (27.3 g/day on average by the FFQ vs. 25.7 g/day on average by a 9-day diet record (22)) and that only 1 baseline measurement was available. However, the correlation between dietary fiber intake as estimated by the FFQ and the 9-day diet record was high (0.74) (22), and the FFQ was found to be reproducible over a period of at least 5 years (23).

In conclusion, we observed frequent bowel movements to be associated with an increased risk of colorectal cancer in men and constipation to be associated with a decreased risk. Subsite analyses revealed associations with rectal cancer risk in particular. There was no evidence of effect modification by dietary fiber intake.

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Author affiliations: Department of Epidemiology, GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, the Netherlands (Colinda C. J. M. Simons, Leo J. Schouten, Matty P. Weijenberg, Piet A. van den Brandt); and Department of Prevention and Health, TNO Quality of Life, Netherlands Organisation for Applied Scientific Research, Leiden, the Netherlands (R. Alexandra Goldbohm).

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