



Prospective Study of Bowel Movement, Laxative Use, and Risk of Colorectal Cancer among Women

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The authors prospectively examined the association between bowel movement frequency, laxative use, and the risk of colorectal cancer in 84,577 women of the Nurses' Health Study living in the United States, 36–61 years of age and free of cancer in 1982. Between 1984 and 1996, 611 incident cases of colorectal cancer were documented. After controlling for age, body mass index, fiber intake, postmenopausal status and hormone use, physical activity, and use of laxatives, the relative risks associated with having bowel movements every third day or less, compared with those with bowel movements once daily, were 0.94 (95% confidence interval (CI): 0.69, 1.28) for colorectal cancer, 0.88 (95% CI: 0.62, 1.26) for colon cancer, and 1.18 (95% CI: 0.63, 2.20) for rectal cancer. Compared with women who never used laxatives, the multivariate relative risks associated with weekly to daily laxative use were 1.00 (95% CI: 0.72, 1.40) for colorectal cancer, 1.09 (95% CI: 0.76, 1.57) for colon cancer, and 0.68 (95% CI: 0.29, 1.57) for rectal cancer. These findings do not support an association between infrequent bowel movement, laxative use, and risk of colorectal cancer and indicate that simple questions directed at bowel movement frequency are unlikely to enhance our ability to predict colorectal cancer risk. *Am J Epidemiol* 2000;151:958–64.

cathartics; colorectal neoplasms; constipation; prospective studies

It has long been suggested that low bowel movement frequency, by increasing concentrations of carcinogens in the stool and increasing their contact with the gut wall, elevates the risk of colorectal cancer (1–9). In the United States, where colorectal cancer is the third highest cause of cancer mortality (10), 15–20 percent of adults are reported to suffer from constipation, and a similar proportion use laxatives (11–13).

Previous epidemiologic studies, mostly retrospective, have examined bowel movement frequency in relation to the risk of colorectal cancer. These studies tend to show inconsistent results, in part because of the

complexity in characterizing bowel movements (13–24). The customary medical criterion for constipation is an average stool frequency less than three times per week, but the term constipation remains ambiguous and may be used to describe infrequent bowel actions, hard stools, straining, or difficulty in defecation (25–27). The report of no more than two bowel movements per week may be a more reliable and clinically important indicator of abnormal bowel function than the subjective complaint of constipation (24, 28–34).

The widespread use of laxatives further complicates the relation between bowel movement frequency and the risk of colorectal cancer. Possibly, the laxatives used to treat constipation, rather than constipation itself, increase the risk of colorectal cancer (34). Some studies indicate a genotoxic potential of some laxatives (15, 16). Even though infrequent bowel movement and laxative use are widespread, relatively few studies have examined these in relation to colorectal cancer risk, and data from cohort studies are particularly sparse. Thus, we investigated prospectively the association between infrequent bowel movements (every third day or less) and the use of laxatives in relation to incidence of colorectal cancer in US women.

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Abbreviations: CI, confidence interval; RR, relative risk.

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MATERIALS AND METHODS

Study cohort

In 1976, 121,700 female registered nurses aged 30–55 years were enrolled in the Nurses' Health Study by return of a mailed questionnaire. Every 2 years, follow-up questionnaires have been mailed to the participants to update information on risk factors and major medical events. Dietary intake data were collected in 1980, 1984, 1986, and 1990 by means of self-administered, semiquantitative food-frequency questionnaires (35, 36). A total of 90,611 women provided information about their bowel movement frequency in 1982. Possible answers for bowel movement were more than once daily, daily, every other day, every 3–4 days, every 5–6 days, and once a week or less. In the 1982 questionnaire we also queried participants about the use of laxatives, including softeners, bulk agents, and suppositories. Possible answers were laxative use daily, at least once a week, 1–4 times a month, less than once a month, and never. The reasons for laxative use and type of laxatives were not assessed.

Of the 90,611 women who answered the bowel movement frequency and laxative question in 1982, we excluded 924 women who reported a diagnosis of ulcerative colitis and 5,110 women who reported a cancer diagnosis other than nonmelanoma skin cancer prior to 1984 ($n = 84,577$). Through 1996, follow-up was completed for 94.7 percent of potential person-years.

Case ascertainment

On each biennial follow-up questionnaire, we asked whether cancer of the colon or rectum had been diagnosed during the previous 2 years. We also used the National Death Index and the US Postal Service to identify fatalities, and we estimate that more than 98 percent of deaths were ascertained (37). When a study participant (or next of kin for decedents) reported a diagnosis of cancer of the colon or rectum on our follow-up questionnaire, we asked her (or next of kin) for permission to obtain relevant hospital records and pathology reports. A study physician, blinded to the exposure information, reviewed the medical records to extract information on the histologic type, the anatomic location, and the stage of the cancer. Proximal colon cancers were defined as those from the cecum to, and including, the splenic flexure; distal colon cancers were defined as those in the descending and sigmoid colon. Cancers other than adenocarcinoma were excluded.

To minimize any influence of symptoms of colon cancer on the exposures of interest, we considered

cases diagnosed 2 years (1984) or more after exposure assessment (1982). The 12-year follow-up analysis from 1984 to 1996 of 84,439 women included 611 incident cases of colorectal cancer (428 colon cancer, 126 rectal cancer, and 57 site unspecified).

Statistical analysis

Bowel movement frequency and the use of laxative were analyzed as categorical variables according to the questions asked in 1982. Before any exclusions, the relatively few women who reported bowel movements every 5–6 days ($n = 870$) and once a week or less ($n = 282$) were combined with those who reported bowel movement every 3–4 days ($n = 6,876$). To minimize any influence of symptoms of colorectal cancer on the exposures of interest, we excluded the first 2 years of follow-up and computed person-time of follow-up from the month of return of the 1984 questionnaire to the date of colorectal cancer diagnosis, death from any cause, or May 31, 1996, whichever came first. For bowel movement frequency and laxative use, person-months of follow-up were allocated according to status in 1982. Relative risks estimated by odds ratios and their 95 percent confidence intervals for each category were calculated using the daily category for bowel movement and the never-use category for laxative use as the comparison groups. Trends were tested by using midpoint values of each category of bowel movement frequency or laxative use frequency as a continuous variable in a logistic regression model. The p values for the trends are two sided.

We used pooled logistic regression models to control simultaneously for several potentially confounding variables. This approach has been used in prospective cohort analyses with repeated measures of exposures and has been shown to be asymptotically equivalent to Cox regression analysis if the time intervals are short and the probability of an event is small for each time interval (38). We included in the models covariates that are a priori potential risk factors for colorectal cancer and possibly related to bowel movement physiology, including age (in six 5-year categories), body mass index (in quintiles), fiber intake (in quintiles), and nonoccupational physical activity (quintiles of metabolic equivalents per week). We also considered menopausal status and hormone replacement use as covariates, because use of postmenopausal hormones is related to lower colorectal cancer risk in this cohort (39) and could influence bowel movement physiology. Because these variables could either be true confounders (independent risk factors) or determinants of bowel movement frequency, we considered models both with and without these factors. In a subanalysis, we checked for a change in the relative risks by adding aspirin intake (yes/no), multivitamin use

(yes/no), alcohol intake (in quintiles), and consumption of red meat (beef/pork/lamb as a main dish in six categories) to the model. Except for age, body mass index, postmenopausal status, and hormone use, which were updated biennially, we used the covariate status as of 1984.

In an additional analysis we excluded women who had undergone endoscopic examination before the study began ($n = 12,726$), because a difference in the rate of removal of premalignant adenomas by bowel movement frequency or laxative use status could bias results. Our major endpoints were total colorectal, colon, and rectal cancer; we also examined proximal and distal colon cancers separately as etiologic differences could exist by subsite.

RESULTS

During 991,660 person-years of follow-up over a 12-year period (1984 through 1996), we documented

428 cases of colon cancer and 126 cases of rectal cancer among 84,439 women; 57 cases had unspecified sites. These were included with colon cancers because most cases of colorectal cancer were in the colon, and results with or without these were very similar. Within the study population, 8.6 percent reported infrequent bowel movement (every third day or less), and 27.9 percent reported use of laxatives, 5.3 percent on a weekly to daily basis. Table 1 presents age-standardized risk factors for colorectal cancer and other selected factors according to bowel movement and laxative use in 1982. Women who reported bowel movements more than once daily or daily were slightly older, and women who reported use of laxatives were slightly younger. Compared with women with daily bowel movements, those with infrequent bowel movements had lower total energy intake, a lower body mass index, and lower alcohol intake and were more likely to use aspirin and less likely to exercise regularly and use multivitamins. Compared with women

TABLE 1. Characteristics* of the study participants according to bowel movement and use of laxatives, Nurses' Health Study questionnaire, 1982

	Age (years)†	Body mass index‡	Total energy intake (kcal/day)	Alcohol intake (g/day)§	Dietary intake (g/day)			
					Protein	Carbohydrates	Fat¶	Dietary fiber
Bowel movement frequency								
>1/day ($n = 8,461$)	49.5	26.1	1,832	7.3	71.3	185	56.2	16.1
Daily ($n = 53,432$)	49.0	24.5	1,751	7.2	71.5	185	56.1	16.4
Every 2 days ($n = 15,378$)	47.5	24.1	1,715	6.3	71.0	187	56.4	16.4
Every 3 days or less ($n = 7,306$)	47.5	24.0	1,670	5.9	70.4	186	57.3	16.0
Laxative use								
Weekly-daily ($n = 5,081$)	48.3	24.1	1,725	6.7	71.9	186	56.2	17.0
Monthly ($n = 3,790$)	49.4	24.4	1,734	6.9	71.6	186	56.4	16.7
Less than monthly ($n = 14,467$)	49.2	24.7	1,729	6.7	71.7	185	56.4	16.5
Never ($n = 61,239$)	50.4	24.6	1,751	7.1	71.1	186	56.2	16.3
	Aspirin intake (%)§	Use of multi-vitamins (%)§	Regular physical activity (%)	Use of hormones (%)	Current smoking (%)	Family history of colorectal cancer (%)	Laxative use weekly to daily (%)	Bowel movement frequency every 3 days or less (%)
Bowel movement frequency								
>1/day ($n = 8,461$)	28.1	39.5	41.5	10.4	27.2	9.1	4.0	
Daily ($n = 53,432$)	26.0	37.7	43.6	9.5	28.2	8.5	4.2	
Every 2 days ($n = 15,378$)	23.7	35.7	41.4	9.9	23.2	8.9	8.6	
Every 3 days or less ($n = 7,306$)	22.6	32.7	37.6	11.4	24.5	8.4	16.2	
Laxative use								
Weekly-daily ($n = 5,081$)	21.7	45.7	43.3	15.0	25.1	9.7		23.2
Monthly ($n = 3,790$)	19.9	41.9	43.1	13.0	25.5	8.6		27.4
Less than monthly ($n = 14,467$)	22.3	39.2	42.1	11.5	26.9	8.7		12.8
Never ($n = 61,239$)	27.0	35.6	42.5	8.7	27.2	8.5		5.3

* Values are means directly standardized according to the age distribution at baseline of the respective cohort in its entirety. Dietary values represent the mean energy-adjusted intake.

† Mean age in 1982 not standardized.

‡ Weight (kg)/height (m)².

§ Use in 1980.

¶ Sum of saturated, monounsaturated, and polyunsaturated fatty acids.

who never used laxatives, women who used laxatives weekly to daily were more likely to use postmenopausal hormones and multivitamins and less likely to smoke (table 1).

Bowel movement frequency

Age was by far the most powerful risk factor for colorectal cancer, but the age-adjusted and multivariate relative risks showed similar results. On the basis of the 1982 questionnaire and follow-up from 1984 to 1996, the multivariate relative risks for individuals with infrequent bowel movements, relative to those with daily bowel movements, were 0.94 (95 percent confidence interval (CI): 0.69, 1.28) for all colorectal cancer, 0.88 (95 percent CI: 0.62, 1.26) for colon cancer only, and 1.18 (95 percent CI: 0.63, 2.20) for rectal cancer only (table 2). Excluding women who had had a colonoscopy or sigmoidoscopy prior to 1984 led to similar results: the multivariate relative risk was 0.88 (95 percent CI: 0.63, 1.23) for all colorectal cancer, 0.79 (95 percent CI: 0.53, 1.17) for colon cancer only, and 1.23 (95% CI: 0.66, 2.30) for rectal cancer only. No trend was evident for any of the endpoints. There were no changes in the relative risks after adding aspirin use, multivitamin use, alcohol intake, and red meat consumption to the model. Among women who reported bowel movement more than once a day, we noted a slight suggestion of a decreased risk for distal colon cancer and rectal cancer, but this was not statistically significant (table 2). The subanalysis excluding all women who used laxatives showed similar results as for the whole sample (multivariate relative risk (RR) for colorectal cancer = 0.95, 95 percent CI: 0.60, 1.50 for bowel movements every third day or less).

Laxatives

No significant association was seen between laxative use and colorectal cancer risk. The age-adjusted and multivariate odds ratio showed similar results. The multivariate relative risk for women who used laxatives weekly to daily relative to those who never used laxatives was 1.00 (95 percent CI: 0.72, 1.40) for colorectal cancer, 1.09 (95 percent CI: 0.76, 1.57) for colon cancer, and 0.68 (95 percent CI: 0.29, 1.57) for rectal colon cancer. For distal colon cancer, monthly laxative use was associated with an elevated risk (RR = 1.67, 95 percent CI: 0.95, 2.94), but with weekly to daily laxative use this relative risk was attenuated (RR = 1.27, 95 percent CI: 0.74, 2.20) (table 3). No trend was evident. The exclusion of women who reported previous sigmoidoscopy or colonoscopy before 1984 resulted in slightly stronger, yet nonsignificant associations: relative

TABLE 2. Relative risks of colorectal cancer according to bowel movement in a prospective study of women, Nurses' Health Study, 1982-1996

	No. of cases	Relative risk (age adjusted)	Relative risk (multivariate)*	95% confidence interval
<i>Colorectal cancer (n = 611)</i>				
Bowel movement				
>1/day	57	0.83	0.82	0.62, 1.09
Daily†	406	1.00	1.00	
Every 2 days	100	0.96	0.96	0.77, 1.20
Every 3 days or less	48	0.96	0.94	0.69, 1.28
<i>p</i> for trend‡		0.43		
<i>Colon cancer (n = 485)</i>				
Bowel movement				
>1/day	48	0.90	0.89	0.65, 1.20
Daily†	317	1.00	1.00	
Every 2 days	84	1.04	1.03	0.80, 1.31
Every 3 days or less	36	0.93	0.88	0.62, 1.26
<i>p</i> for trend		0.60		
<i>Proximal colon cancer (n = 213)</i>				
Bowel movement				
>1/day	23	1.03	1.04	0.67, 1.63
Daily†	132	1.00	1.00	
Every 2 days	38	1.15	1.15	0.80, 1.66
Every 3 days or less	20	1.26	1.26	0.77, 2.04
<i>p</i> for trend		0.46		
<i>Distal colon cancer (n = 202)</i>				
Bowel movement				
>1/day	15	0.65	0.64	0.37, 1.09
Daily†	137	1.00	1.00	
Every 2 days	37	1.04	0.99	0.68, 1.44
Every 3 days or less	13	0.76	0.67	0.38, 1.21
<i>p</i> for trend		0.36		
<i>Rectal cancer (n = 126)</i>				
Bowel movement				
>1/day	9	0.60	0.59	0.30, 1.18
Daily†	89	1.00	1.00	
Every 2 days	16	0.68	0.72	0.42, 1.23
Every 3 days or less	12	1.08	1.18	0.63, 2.20
<i>p</i> for trend		0.49		

* Adjusted for age, body mass index, fiber intake, physical activity, postmenopausal status and hormone use, and use of laxatives.

† Reference category.

‡ *p* for trend calculated by using the median of each category of bowel movement as a continuous variable in the pooled logistic regression model.

risks for daily to weekly users were 1.04 (95 percent CI: 0.72, 1.49) for colorectal cancer, 1.16 (95 percent CI: 0.78, 1.72) for colon cancer, 0.65 (95 percent CI: 0.26, 1.63) for rectal cancer, and 1.30 (95 percent CI: 0.71, 2.39) for distal colon cancer. With laxatives, too, there were no changes in the relative risks after adding aspirin use, multivitamin use, alcohol intake, and red meat consumption to the model.

Thus, for regular laxative users a slight but non-significant association was found for colon cancer. This association was limited to distal colon cancer. We

TABLE 3. Relative risks of colorectal cancer according to laxative use in a prospective study of women, Nurses' Health Study, 1982-1996

	No. of cases	Relative risk (age adjusted)	Relative risk (multivariate)*	95% confidence interval
<i>Colorectal cancer (n = 611)</i>				
Use of laxatives				
Never†	433	1.00	1.00	
Less than monthly	108	0.95	0.96	0.78, 1.19
Monthly	32	1.11	1.14	0.79, 1.65
Weekly-daily	40	0.96	1.00	0.72, 1.40
<i>p</i> for trend‡		0.83		
<i>Colon cancer (n = 485)</i>				
Use of laxatives				
Never†	338	1.00	1.00	
Less than monthly	86	0.99	1.00	0.79, 1.27
Monthly	27	1.19	1.24	0.83, 1.86
Weekly-daily	34	1.03	1.09	0.76, 1.57
<i>p</i> for trend		0.62		
<i>Proximal colon cancer (n = 213)</i>				
Use of laxatives				
Never†	149	1.00	1.00	
Less than monthly	41	1.05	1.05	0.74, 1.49
Monthly	10	0.99	0.96	0.50, 1.84
Weekly-daily	13	0.88	0.86	0.48, 1.54
<i>p</i> for trend		0.64		
<i>Distal colon cancer (n = 202)</i>				
Use of laxatives				
Never†	137	1.00	1.00	
Less than monthly	36	1.03	1.04	0.72, 1.52
Monthly	14	1.54	1.67	0.95, 2.94
Weekly-daily	15	1.16	1.27	0.74, 2.20
<i>p</i> for trend		0.55		
<i>Rectal cancer (n = 126)</i>				
Use of laxatives				
Never†	95	1.00	1.00	
Less than monthly	20	0.83	0.83	0.51, 1.35
Monthly	5	0.80	0.79	0.31, 1.97
Weekly-daily	6	0.67	0.68	0.29, 1.57
<i>p</i> for trend		0.35		

* Adjusted for age, body mass index, fiber intake, physical activity, postmenopausal status and hormone use, and bowel movement frequency.

† Reference category.

‡ *p* for trend calculated by using the median of each category of intake as a continuous variable in the pooled logistic regression model.

found a slight indication of a decreased risk for rectal cancer for all categories of laxative users, but again this result was not statistically significant.

Infrequent bowel movements and laxative use

In a further subanalysis we classified women simultaneously by both bowel movement frequency and laxative use. In a multivariate analysis, the relative risk for colorectal cancer for women who had both infrequent bowel movements and weekly to daily use of laxatives was 0.68 (95 percent CI: 0.31, 1.53) com-

pared with those who had daily bowel movements and never used laxatives.

DISCUSSION

In these prospective data, self-reported frequency of bowel movements was not associated with an increase in the incidence of colorectal cancer. This result was consistent for colon and rectal cancer. Most of the previous data on bowel movement and colorectal cancer risk have been based on case-control studies. A recent meta-analysis has summarized results of 14 published case-control studies and demonstrated a statistically significant increased risk for colorectal cancer with constipation or infrequent bowel movements (pooled odds ratio = 1.48) (17). The findings were stronger for colonic than for rectal cancers. However, the results across the individual studies were relatively inconsistent. Another recently published case-control study found a positive association between colon cancer and weekly to monthly constipation (RR = 2.0) and more than weekly constipation (RR = 4.4) (19). The results of the meta-analysis and the case-control study are contrary to our findings. This may be due to the fact that, in the case-control study by Jacobs and White (19) as well as in the case-control studies included in the meta-analysis (17), the assessment of the exposure of interest may not accurately reflect bowel movement frequency, as described below. Furthermore, the possibility of biased recall of bowel function by a patient with colorectal cancer cannot be excluded in some of the case-control studies. In an ecologic study of fecal weights and transit times in rural and urban Finnish and Danish populations with markedly different cancer incidence, no difference between the two populations in either fecal weight or intestinal transit time was found (20). The inconsistency of existing data concerning low bowel movement frequency and risk of colorectal cancer may be partly explained by the fact that the relevant time period when risk factors act in the process of cancer development is often unknown. Colorectal cancer entails a long process occurring over decades, but most studies have focused on the time period relatively shortly before the diagnosis.

In the above-mentioned meta-analysis (17), a statistically significant increased risk of colorectal cancer was seen with the use of laxatives. However, the authors state that, since laxative use was associated with lower odds ratios (pooled odds ratio = 1.46) than for various dietary components, this excess risk could reflect the confounding influence of underlying dietary habits. As for bowel movement, the included studies assessed laxative use in diverse ways and for various durations of use. While some assessed laxative use in general, others considered use of specific laxa-

tives such as anthraquinones and phenolphthalein-containing laxatives. It is likely that different types of laxatives would have varying effects, if any, regarding cancer. An increased risk has been found in two case-control studies for the use of anthraquinone laxatives (RR = 3.04, 95 percent CI: 1.18, 4.90) (21) and for phenolphthalein-containing laxatives (RR = 1.37; nonsignificant) (16). For these two case-control studies, recall bias cannot be excluded. Jacobs et al. also reported a positive association among constipation, laxative use, and colorectal cancer risk. When adjusted for each other, the association for laxative disappeared while the association for constipation remained strong (19), suggesting that laxative use may have been acting as a marker of constipation. Three other case-control studies and one retrospective cohort study found no association between laxative use and colorectal cancer (22–24). In general, among the studies that found an association between use of laxatives and the risk of colorectal cancer, the association was stronger for women than for men (18, 23).

We observed little relation between laxative use and risk of colorectal cancer. A weak and not statistically significant direct association was seen between monthly laxative use and distal colon cancer and an inverse association between monthly and weekly to daily laxative use and proximal and rectal cancer. However, considering the low number of cases for these specific cancer sites, the attenuation by greater laxative use for distal colon cancer, the fact that no trend was evident, and that no relative risks were statistically significant, we believe these findings are most probably a result of chance. Furthermore, the weak inverse association between laxative use and some sites of colorectal cancer may be caused by mechanisms other than bowel movement frequency. Laxatives influence intestinal pH and modify the metabolism of the intestinal flora, factors that may modify colorectal cancer risk (40).

The major strengths of our study are its prospective nature, the ability to control for other known or suspected risk factors for colorectal cancer, and the relatively large size. A limitation of this study is that the questions about bowel movement and the use of laxatives were only asked once without updating during ongoing study. Some authors consider bowel movement frequency to be the most adequate question to assess bowel transit time (12, 28–34). Others disagree, assuming that people are inaccurate in recalling their bowel frequency; however, the study population observed by these authors comprised patients with irritable bowel syndrome, a disease where the complaint is mostly loose stools (41–45). In contrast to constipation, bowel movement frequency is clearly defined,

and we consider this the variable that can most feasibly assess bowel transit time in larger studies. Although the self-report of bowel movement frequency and laxative use could not be directly validated, the nurses have been shown to report highly accurate medically related information for a variety of conditions. The relations between frequency of bowel movement transit time and colorectal cancer may be complex, but from a practical perspective our results indicate that a single assessment of bowel movement frequency is unlikely to be informative regarding subsequent risk of colorectal cancer. Another limitation is that we could study only the overall impact of laxative use and not the effects of specific types of laxatives.

In conclusion, these prospective data do not support any substantial risk of colorectal cancer associated with infrequent bowel movement or laxative use. Further studies are needed to determine whether specific types of laxatives and alternative assessment of bowel transit time besides bowel movement frequency influence the risk of colorectal cancer.

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