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## Prospective cohort studies of bowel movement frequency and laxative use and colorectal cancer incidence in US women and men

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### Abstract

**Purpose**—The associations between bowel movement frequency, laxative use and colorectal cancer incidence remain uncertain. No published studies have accounted for potential latency between these factors and colorectal cancer onset.

**Methods**—We prospectively examined these associations among 88,173 women in the Nurses' Health Study (NHS, 1982-2010) and 23,722 men in the Health Professionals Follow-up Study (HPFS, 2000-2010). Cox proportional hazards regression models were used to estimate multivariable hazard ratios (HRs, 95% CIs). We conducted time lagged analyses to evaluate the potential latency in the NHS.

**Results**—We documented 2,012 incident colorectal cancer cases. The HRs (95% CIs) for infrequent bowel movement relative to daily were 0.86 (95% CI: 0.71-1.04) in women and 0.81 (95% CI: 0.48-1.37) in men. The HRs for weekly to daily relative to never laxative use were 0.98 (95% CI: 0.81-1.20) in women and 1.41 (95% CI: 0.96-2.06) in men. In women, the HRs for every 3 days or less bowel movement relative to daily were 0.87 (95% CI: 0.59-1.27) for colorectal cancers that developed within 10 years of assessment, 1.03 (95% CI: 0.85-1.26) for 11-18 years after assessment, and 0.73 (95% CI: 0.54-1.01) for 19-28 years after assessment. The corresponding HRs for weekly to daily relative to never laxative use were 0.93 (95% CI: 0.63-1.37), 1.03 (95% CI: 0.74-1.44), and 0.98 (95% CI: 0.71-1.35), respectively.

**Conclusion**—Bowel movement frequency and laxative use appear not to be associated with colorectal cancer risk in this study.

### Keywords

bowel movement frequency; laxative use; colorectal cancer; incidence; prospective study; latency

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## Introduction

It has been estimated that approximately 15-20% of US adults suffer from constipation and a similar proportion of individuals use laxatives [1]. Infrequent bowel movements may increase colorectal cancer risk because it may increase concentration and contact time of potential carcinogens in the large bowel [2]. Given that colorectal cancer remains the third most common cancer in US adults [3], any association between this cancer and bowel movement frequency or laxative use has public health implications.

To date, the limited epidemiologic studies that specifically examined these associations have yielded inconsistent results [4-14]. The case-control studies that assessed information on bowel movement and laxative use after cancer developed may be subject to potential bias since disease status may have influenced bowel movement frequency or use of laxatives [4-8]. Prior cohort studies have generally focused on the assessments of bowel movement frequency or laxative use relatively shortly before the colorectal cancer diagnosis [9-14] and results have been inconsistent. No published prospective cohort studies have accounted for the potential latency between these factors and colorectal cancer onset. Importantly, the relevant time period when bowel movement frequency or use of laxatives may act in the process of colorectal cancer development remains unknown.

Thus, to address these limitations of prior studies, we conducted a prospective study of bowel movement frequency and laxative use within two large, long-running cohorts, the female Nurses' Health Study (NHS), and the male Health Professionals Follow-up Study (HPFS). Previously, we reported null associations between bowel movement frequency and laxative use and colorectal cancer risk in the NHS [14], which encompassed only 611 incident cases over 12 years of follow-up. In the current analysis, we expand on our initial report by including 1,737 incident cases over 28 years of follow-up in the NHS as well as 227 incident cases over 10 years in the parallel HPFS. This long follow-up period and large number of cases allowed us to conduct time lagged analyses to evaluate potential latency between these factors and colorectal cancer onset.

## Materials and methods

### Study population

The Nurses' Health Study (NHS) includes 121,700 registered female nurses who were aged 30 to 55 years at baseline in 1976 in the US [15]. The Health Professionals Follow-up Study (HPFS) includes 51,529 US male professionals who were aged 40 to 75 years at baseline in 1986 [16]. Participants in each cohort have been sent questionnaires every two years since 1976 and 1986 respectively, to collect information on demographic, lifestyle factors, medical history, and disease outcomes. The follow-up rate has been greater than 90% for each cohort. Both studies have been approved by the institutional review board at the Brigham and Women's Hospital and the Harvard School of Public Health, Boston, Massachusetts. Return of the questionnaires was considered to imply informed consent and written consent from each participant were also collected to obtain and review medical records.

Because information on bowel movement frequency and laxative use was not assessed until 1982 in the NHS and 2000 in the HPFS, we used 1982 as baseline for the NHS and 2000 as baseline for the HPFS. We excluded participants with ulcerative colitis (n = 1084 in women, n = 250 in men), history of cancer diagnosis before baseline (except for non-melanoma skin cancer, n = 5,206 in women, n = 11,579 in men), or missing data on bowel movement or laxative use (n = 15,701 in women, n = 3,885 in men), leaving a total of 88,173 women and

23,722 men for this analysis. Participants who did not answer the questions on bowel movement frequency or laxative use did not differ substantially from respondents according to age, body mass index, physical activity, endoscopy screening, family history of colorectal cancer, alcohol consumption, and major dietary factors.

### **Assessment of bowel movement frequency and laxative use**

In the 1982 questionnaire in the NHS and in the 2000 questionnaire in the HPFS, participants were asked to report the frequency of bowel movement; 7 possible answers were: more than once daily, daily, every other day, every 3-4 days, every 5-6 days, and once a week or less. We also asked participants how often they use laxatives including softeners, bulking agents, and suppositories; 5 possible answers were: daily, at least once per week, 1-4 times per month, less than 1 time per month, and never.

### **Identification of incident colorectal cancer cases**

The ascertainment of colorectal cancer cases has been described in detail elsewhere [17]. In brief, participants in each cohort reported cancer and other disease outcomes via biennial questionnaires. Researchers obtained participants' permission to collect their medical records and pathological reports. While blinded to exposure information, the researchers abstracted the information on anatomic location, stage, and histological type of the cancer. Colorectal cancer and sub-sites were defined according to the International Classification of Diseases, Ninth Revision [ICD-9] [18].

### **Assessment of other covariates**

We obtained information on potential colorectal cancer risk factors such as height, body weight, physical activity (MET-hrs/wk), cigarette smoking, aspirin use, family history of colorectal cancer, and menopausal status and postmenopausal hormone use (women only) via the biennial questionnaires. In addition, dietary factors were assessed using validated food frequency questionnaires in the NHS [19] and in the HPFS [20]. These factors included consumption of red meat, processed meat, alcohol, fiber, folate, calcium, and vitamin D.

### **Statistical analyses**

We calculated person-time for each participant from the date of baseline questionnaire return (1982 for the NHS and 2000 for the HPFS) to the date of death, loss to follow-up, colorectal cancer diagnosis, or the end of follow-up (May 31, 2010 for the NHS; January 1, 2010 for the HPFS), whichever came first. To have reasonable number of cases in each category, bowel movement frequency was categorized into 4 categories in the NHS: more than once daily, daily, every 2 days, and every 3 days or less; and 3 categories in the HPFS: more than once daily, daily, and every 2 days or less. Regarding the laxative use, we used 4 categories in the NHS: never, less than monthly, monthly, weekly to daily; and 3 categories in the HPFS: never, less than monthly, and monthly to daily. As previously described [14], we tested for trends using midpoint values of each category of bowel movement frequency or laxative use frequency as continuous variables.

We used a Cox proportional hazards regression model [21] to calculate hazard ratios (HRs, 95% CIs) and adjusted simultaneously for age (in months) and year of questionnaire return. We observed no violation of the proportional hazard assumption based on the likelihood ratio test that compared the model with and without the interaction terms between bowel movement frequency or laxative use and age or follow-up time. We conducted all analyses using the SAS software (Version 9.2; SAS Institute Inc). All statistical analyses were two-sided with a *p*-value less than 0.05 indicating significance.

In addition to age, we adjusted for established or potential risk factors for colorectal cancer in multivariable models (see Table 2 for these variables and the categorizations). For the dietary factors, we used the data from the baseline food frequency questionnaires (i.e., 1980 for the NHS and 2000 for HPFS). To evaluate different latency periods in women, we used bowel movement frequency or laxative use assessed in 1982 to predict the risk of colorectal cancer within 10 years of assessment, 11-18 years after assessment, and 19-28 years after assessment.

We conducted sensitivity analysis by excluding participants who had colonoscopy or sigmoidoscopy examination before baseline because a difference in the rate of removal of premalignant adenomas by bowel movement frequency or laxative use might bias the results [14]. To further evaluate the robustness of our results, we conducted additional analysis in which we adjusted for bowel movement and laxative use simultaneously in the same multivariable models. In addition, we used cross classified variable to calculate the HRs among participants with both infrequent bowel movement and laxative use. Lastly, we excluded participants who used laxatives when we examined the associations with bowel movement frequency.

We also examined whether the associations differ by levels of physical activity (medians in each cohort), total fiber intake (medians in each cohort), and menopausal status (premenopausal vs. postmenopausal; women only). We constructed cross-product terms between bowel movement frequency or laxative use frequency (i.e., medians of each category) and these factors (i.e., dichotomized variables) and tested whether beta-coefficients of the cross product terms were statistically significant using a Wald test.

## Results

We documented a total of 2,012 incident colorectal cancer cases including 1,737 cases from 1982-2010 in the NHS, and 275 cases from 2000-2010 in the HPFS. Selected lifestyle and potential confounding factors were compared across categories of bowel movement or laxative use (Table 1). Approximately 9% women and 2% men reported infrequent bowel movement (i.e., every 3 days or less), and 18% women and 7% men reported bowel movement every other day. About 28% women and 19% men reported laxative use in these cohorts, 6% in women and 8% in men on a weekly to daily basis. Compared to women reporting daily bowel movement, those with infrequent bowel movement (i.e., every 3 days or less) were slightly younger, had low physical activity level, low intakes of total energy, alcohol, total calcium, total folate, total vitamin D, total fiber, and less likely to use multivitamins but more likely to use aspirin and laxatives. Compared to women who never used laxative use, women who used laxatives weekly to daily were older, more likely to have infrequent bowel movement, use aspirin and multivitamins. Similar pattern was observed in men (Table 1).

The HRs of colorectal cancer in relation to bowel movement frequency are presented in Table 2. In both men and women, age-adjusted results were essentially the same as multivariable-adjusted results and thus only the multivariable results are presented. Bowel movement frequency was not associated with colorectal cancer risk in each cohort. In women, compared to those with daily bowel movement, women with infrequent bowel movement (i.e., every 3 days or less) had a multivariable HR of 0.86 (95% CI: 0.71, 1.04) (Table 2). Excluding women who had had a colonoscopy or sigmoidoscopy prior to 1982 yielded similar results (HR = 0.85, 95% CI: 0.70, 1.03). Similar null results were observed in men (every 2 days or less vs. daily HR = 0.81, 95% CI: 0.48, 1.37) and among subgroup excluding history of colonoscopy or sigmoidoscopy (HR = 0.55, 95% CI: 0.23, 1.33). In addition, bowel movement frequency was not associated with risk of colorectal cancer when

participants who used laxatives were excluded; the multivariable HRs were 0.86 in women (every 3 days or less vs. daily, 95% CI: 0.65, 1.14) and 1.04 in men (every 2 days or less vs. daily, 95% CI: 0.55, 1.95).

We found no significant associations between laxative use and colorectal cancer risk in each cohort (Table 3). No trend was evident and similar null results were observed for cancer sub-sites. Results were similar after exclusion of participants with history of colonoscopy or sigmoidoscopy (data not shown). Adjusting for bowel movement frequency and laxative use simultaneously yielded null results (data not shown).

In a further subgroup analysis, compared with those who had daily bowel movements and never used laxatives, the multivariable HRs for colorectal cancer for participants who had both infrequent bowel movements and weekly to daily use of laxatives were 0.80 (95% CI: 0.51, 1.26) in women and 0.75 (95% CI: 0.27, 2.10) in men.

As shown in Table 4, we found no significant associations when we evaluated the associations between bowel movement frequency or laxative use and risk of colorectal cancer diagnosed during years of 1-10, 11-18, or 19-28. Finally, no evident patterns were seen when we examined the potential interactions with physical activity, total fiber intake, or by menopausal status (all  $p$ -value for interaction  $> 0.05$ , data not shown).

## Discussion

In these two large cohorts of US women and men, bowel movement frequency and laxative use appear not associated with colorectal cancer incidence. Our current study, an extended analysis of the NHS and a new analysis of the HPFS further suggested that bowel movement and laxative use, even assessed within or more than a decade before diagnosis, were not associated with colorectal cancer risk. The null results were consistent within cancer sub-sites.

Epidemiologic studies examining the association between constipation and colorectal cancer risk have reported mixed results. A meta-analysis of 9 case-control studies (cases  $n = 5$  to 296 in constipation group) published in 1993 reported a modest, yet significant, association between constipation and higher risk of colorectal cancer (summary OR = 1.48, 95% CI: 1.32, 1.66) [4]. There was significant between-studies heterogeneity ( $p < 0.001$ ) because 4 out of 9 case-control studies found statistically significant associations [4]. As discussed by the authors, it remains uncertain whether the reported constipation are symptoms of colorectal cancer itself or due to recall bias that may have influenced the results [4]. Importantly, self-reported constipation might not be an appropriate indicator for bowel transit time because participants who reported constipation pass bowel movement daily or more frequently than daily [1]. As shown in a case-control study [7], 93% healthy controls with less than 3 stools per week and 54% of participants with  $\geq 3$  stools per week reported constipation. Thus, self-reported constipation had high sensitivity but poor specificity for identifying persons with constipation [7] and self-reported constipation was considered less accurate than reported stool frequency [7,22]. Given 94-99% of healthy individuals report having a bowel movement varies 3 times per day to 3 times weekly [1], the conventional definition of constipation is an average stool frequency less than three times per week. This definition is currently used as a more reliable way to measure constipation. Among that meta-analysis, only 2 studies used infrequent bowel movement to define constipation status and thus, misclassification of constipation may have biased the results in any direction. Results from other subsequent case-control studies of self-reported constipation or bowel movement frequency have also been inconsistent [5-8].

To our knowledge, four cohort studies [9-12] have examined the associations with constipation since our initial report [14]. Our null results of infrequent bowel movement and colorectal cancer were consistent with those observed in the Miyagi Cohort Study (n = 160 cases in men, 91 cases in women; bowel movement less than daily vs. daily, RR = 1.30, 95% CI: 0.89,1.88) [12] and the Japan Public Health Center-based Prospective Study [10] (two to three bowel movements per week vs. daily, RR = 0.75, 95% CI: 0.49, 1.13 in women, n= 176 cases; RR = 0.97, 95% CI: 0.61,1.55 in men, n = 303 cases). Another report from the Japan Collaborative Cohort Study [9] found null association between frequency of bowel movement and colorectal cancer in men (n = 270 cases). Among women (n = 379 cases), a significant association was observed (bowel movement every 6 days or less vs. at least daily, RR = 2.47, 95% CI: 1.01-6.01) but results were only based on 5 cases. Interestingly, a recent study conducted in the Netherland (n= 1207 cases in men) reported a significant inverse association (constipation sometimes or more often vs. never, RR = 0.57, 95% CI: 0.35-0.90) [11]. As shown above, although all cohort studies used frequency of bowel movement to define constipation, the comparison group differed across studies that made direct comparisons challenging. Furthermore, limited studies have examined different bowel habits [6,8] such as stool consistency, diarrhea or examined the associations with adenomas [22,23]. An undiagnosed cancer might influence bowel movement frequency causing a bias (reverse causation). In addition, it is possible that bowel movement function influences only early stage of colorectal carcinogenesis (i.e., adenoma formation), and an association with cancer would only be observed after a sufficiently long time lag. We thus conducted time lagged analyses to evaluate potential latency in women but no significant associations were seen. Collectively, current epidemiologic studies appear not to support an important association between constipation and colorectal cancer risk [24].

About 15-20% individuals use laxatives in the US on a regular basis whether or not constipation is a problem, particularly among women for weight control [1,7]. Laxative use might be a marker of constipation because association with laxative use disappeared while association with constipation remained strong when both factors were included simultaneously in the same model in a study [5]. On the other hand, laxatives used in treating constipation may have deleterious effect because some *in vitro* and *in vivo* studies have indicated a carcinogenic potential of some laxatives [25]. In our study, we did not find any significant association between overall laxative use and colorectal cancer risk. These results were in contrast with those reported in the above-mentioned meta-analysis of 11 case-control studies of laxative use (yes vs. no, pooled OR = 1.46, 95% CI: 1.33-1.61) [4]. However, only 4 studies were included in that study reported statistical significant associations and a statistically significant between-studies heterogeneity was observed ( $p < 0.001$ ) [4]. Of note, some subsequently published case-control studies conducted in the US, Europe, and Japan have reported null associations [8,5-7]. In addition, our null results of laxative use were generally consistent with three cohort studies conducted to date on this topic [9,12,13]. The first study conducted in the US found no significant associations (daily use vs. < weekly use OR = 1.32, 95% CI: 0.6, 2.7 in men; and OR = 1.38, 95% CI: 0.7, 2.6 in women) [13]. The second Japan Collaborative Cohort Study [9] also found null results (yes vs. no use OR = 1.28, 95% CI: 0.89, 1.86 in men; and OR = 1.20, 95% CI: 0.85, 1.69 in women). The third Miyagi Cohort Study found null association for laxative user (yes vs. no OR = 1.31, 95% CI: 0.88, 1.95) although frequent users had a significant increased risk (> 2 times/week vs. non-user, OR = 2.75, 95% CI: 1.48, 5.09) but only 11 cases were included in this category [12].

Strengths of this study include its prospective design, long follow-up time with high follow-up rate, the ability to control for multiple colon cancer risk factors, inclusion of both women and men, and the assessment of temporal relationship. Several potential limitations merit consideration. As with all previous epidemiologic studies, information on bowel movement

frequency and laxative use was obtained only once without updating. In addition, we have not queried detailed information on types of laxative use and we cannot exclude effect of a specific type of laxative use on colorectal cancer. Furthermore, we are unable to conduct time lagged analyses in men because of the relatively short follow-up.

In summary, our results do not support an association between bowel movement frequency and laxative use and colorectal cancer risk. Additional large studies with updated data on these factors and assessing different types of laxative use might be informative.

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## References

1. Everhart JE, Liang V, Johannes RS, Fitzsimmons SC, Roth HP, White LR. A longitudinal survey of self-reported bowel habits in the United States. *Dig Dis Sci*. 1989; 34(8):1153–1162.10.1007/bf01537261 [PubMed: 2787735]
2. Burkitt DP. Epidemiology of cancer of the colon and rectum. *Cancer*. 1971; 28 (1):3–13. [PubMed: 5165022]
3. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012; 62(1):10–29.10.3322/caac.20138 [PubMed: 22237781]
4. Sonnenberg A, Muller AD. Constipation and cathartics as risk factors of colorectal cancer: a meta-analysis. *Pharmacology*. 1993; 47:224–233.10.1159/000139862 [PubMed: 8234434]
5. Jacobs EJ, White E. Constipation, laxative use, and colon cancer among middle-aged adults. *Epidemiology*. 1998; 9(4):385–391.10.1097/00001648-199807000-00007 [PubMed: 9647901]
6. Park JY, Mitrou PN, Luben R, Khaw K-T, Bingham SA. Is bowel habit linked to colorectal cancer? - Results from the EPIC-Norfolk study. *Eur J Cancer*. 2009; 45(1):139–145.10.1016/j.ejca.2008.10.002 [PubMed: 19013785]
7. Roberts MC, Millikan RC, Galanko JA, Martin C, Sandler RS. Constipation, laxative use, and colon cancer in a North Carolina population. *Am J Gastroenterol*. 2003; 98(4):857–864.10.1016/s0002-9270(03)00050-9 [PubMed: 12738468]
8. Tashiro N, Budhathoki S, Ohnaka K, Toyomura K, Kono S, Ueki T, Tanaka M, Kakeji Y, Maehara Y, Okamura T, Ikejiri K, Futami K, Maekawa T, Yasunami Y, Takenaka K, Ichimiya H, Terasaka R. Constipation and Colorectal Cancer Risk: The Fukuoka Colorectal Cancer Study. *Asia Pac J Clin Nutr*. 2011; 12 (8):2025–2030.
9. Kojima M, Wakai K, Tokudome S, Tamakoshi K, Toyoshima H, Watanabe Y, Hayakawa N, Suzuki K, Hashimoto S, Ito Y, Tamakoshi A, Grp JS. Bowel movement frequency and risk of colorectal cancer in a large cohort study of Japanese men and women. *Br J Cancer*. 2004; 90(7):1397–1401.10.1038/sj.bjc.6601735 [PubMed: 15054462]
10. Otani T, Iwasaki M, Inoue M, Sasazuki S, Tsugane S. Japan Public Hlth Center B. Bowel movement, state of stool, and subsequent risk for colorectal cancer: The Japan public health center-based prospective study. *Ann Epidemiol*. 2006; 16(12):888–894.10.1016/j.annepidem.2006.03.004 [PubMed: 16882473]
11. Simons CC, Schouten LJ, Weijenberg MP, Goldbohm RA, van den Brandt PA. Bowel movement and constipation frequencies and the risk of colorectal cancer among men in the Netherlands Cohort Study on Diet and Cancer. *Am J Epidemiol*. 2010; 172(12):1404–1414.10.1093/aje/kwq307 [PubMed: 20980354]



12. Watanabe T, Nakaya N, Kurashima K, Kuriyama S, Tsubono Y, Tsuji I. Constipation, laxative use and risk of colorectal cancer: The Miyagi Cohort Study. *Eur J Cancer*. 2004; 40(14):2109–2115.10.1016/j.ejca.2004.06.014 [PubMed: 15341986]
13. Wu AH, Paganinihill A, Ross RK, Henderson BE. Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. *Br J Cancer*. 1987; 55(6):687–694.10.1038/bjc.1987.140 [PubMed: 3620314]
14. Dukas L, Willett WC, Colditz GA, Fuchs CS, Rosner B, Giovannucci EL. Prospective study of bowel movement, laxative use, and risk of colorectal cancer among women. *Am J Epidemiol*. 2000; 151 (10):958–964. [PubMed: 10853634]
15. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health*. 1997; 6:49–62. [PubMed: 9065374]
16. Willett, W. *Nutritional Epidemiology*. 2. Oxford University Press; New York: 1998.
17. Zhang X, Giovannucci EL, Smith-Warner SA, Wu K, Fuchs CS, Pollak M, Willett WC, Ma J. A prospective study of intakes of zinc and heme iron and colorectal cancer risk in men and women. *Cancer Causes Control*. 2011; 22(12):1627–1637.10.1007/s10552-011-9839-z [PubMed: 21909950]
18. Puckett, CD. *Diseases and Procedures Tabular Lists*. Reno: 1986. The Educational Annotation of ICD-9-CM.
19. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985; 122:51–65. [PubMed: 4014201]
20. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*. 1992; 135:1114–1126. [PubMed: 1632423]
21. Cox DR. Regression models and life-tables. *J R Stat Soc*. 1972; 34:187–220.
22. Dukas L, Platz EA, Colditz GA, Willett WC, Giovannucci EL. Bowel movement, use of laxatives and risk of colorectal adenomatous polyps among women (United States). *Cancer Causes Control*. 2000; 11(10):907–914.10.1023/a:1026559624330 [PubMed: 11142525]
23. Longnecker MP, Sandler DP, Haile RW, Sandler RS. Phenolphthalein-containing laxative use in relation to adenomatous colorectal polyps in three studies. *Environ Health Perspect*. 1997; 105(11):1210–1212.10.1289/ehp.971051210 [PubMed: 9370521]
24. Adelstein B-A, Macaskill P, Chan SF, Katelaris PH, Irwig L. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. *BMC Gastroenterology*. 2011;11.10.1186/1471-230x-11-65 [PubMed: 21320314]
25. Van Gorkom BAP, De Vries EGE, Karrenbeld A, Kleibeuker JH. Review article: anthranoid laxatives and their potential carcinogenic effects. *Aliment Pharmacol Ther*. 1999; 13 (4):443–452. [PubMed: 10215727]

Table 1

Baseline age-adjusted characteristics of participants by frequency of bowel movement or laxative use in the Nurses' Health Study (1982) and in the Health Professionals Follow-up Study (2000)

	Frequency of bowel movement			Frequency of laxative use				
	More than once per day (n=9091)	Daily (n=55532)	Every other day (n=15957)	Every 3 days or less (n=7593)	Never (n=63705)	Less than monthly (n=15148)	Monthly (n=3970)	Weekly-daily (n=5350)
<b>The Nurses' Health Study</b>								
Age, years*	49.7(7.1)	49.2(7.2)	47.6(7.1)	47.7(7.1)	48.5(7.2)	49.6(7.2)	49.4(7.1)	50.6(7.0)
Body mass index, kg/m <sup>2a</sup>	26.4(6.0)	24.6(4.5)	24.2(4.1)	24.1(4.0)	24.7(4.7)	24.9(4.5)	24.6(4.4)	24.3(4.3)
Activity, MET-h/week <sup>b</sup>	13.8(22.4)	14.4(21.0)	13.6(19.5)	12.5(19.0)	14.1(21.0)	13.7(20.2)	14.2(18.7)	14.4(20.7)
Regular aspirin use (2 or more tablets/wk), %	41	37	40	44	35	45	52	52
Past smoking, %	27	27	28	28	27	27	29	29
Current smoking, %	28	29	25	27	28	28	27	27
Multivitamin use <sup>c</sup> , %	45	41	40	37	39	45	48	52
Total energy intake, kcal/d	1656(523)	1571(495)	1528(493)	1508(498)	1572(500)	1551(497)	1553(491)	1549(513)
Alcohol, g/day	6.9(12.3)	6.6(10.7)	5.5(9.1)	5.4(9.2)	6.5(10.7)	6.0(9.9)	6.3(9.8)	6.2(10.2)
Total calcium intake <sup>d</sup> , μg/d	741(329)	743(316)	717(298)	697(309)	733(313)	731(312)	730(317)	744(331)
Total folate intake <sup>d</sup> , μg/d	375(281)	369(272)	357(265)	340(252)	359(263)	374(281)	381(279)	404(312)
Total vitamin D <sup>d</sup> , IU/d	343(296)	333(285)	318(273)	303(255)	322(276)	338(283)	342(285)	368(340)
Total fiber <sup>d</sup> , g/d	16.2(5.0)	16.5(4.9)	16.5(4.8)	16.1(4.8)	16.3(4.8)	16.6(4.9)	16.8(4.9)	17.0(5.2)
Red meat, servings/wk	2.7(2.0)	2.6(2.0)	2.5(2.0)	2.6(2.1)	2.6(2.0)	2.6(2.0)	2.5(1.9)	2.5(2.0)
Processed meat, servings/wk	1.2(2.0)	1.2(1.8)	1.1(1.7)	1.1(1.7)	1.2(1.8)	1.2(1.7)	1.1(1.7)	1.1(1.9)
Bowel movement frequency every 3 days or less, %	NA				5	13	28	24
Laxative use weekly to daily, %	4	4	9	17	NA			
<b>The Health Professionals Follow-up Study</b>								
	Frequency of bowel movement			Frequency of laxative use				
	More than once per day (n=6286)	Daily (n=15698)	Every Other day (n=1398)	Every 3 days or less (n=340)	Never (n=19735)	Less than monthly (n=1670)	Monthly (n=380)	Weekly-Daily (n=1937)

	Frequency of bowel movement			Frequency of laxative use				
	More than once per day (n=6286)	Daily (n=15698)	Every Other day (n=1398)	Every 3days or less (n=340)	Never (n=19735)	Less than monthly (n=1670)	Monthly (n=380)	Weekly-Daily (n=1937)
Age, years*	64.1(8.1)	65.2(8.6)	67.2(9.6)	70.0(10.0)	64.4(8.3)	69.2(9.1)	70.7(9.6)	67.9(9.3)
Body mass index, kg/m <sup>2</sup> <sup>a</sup>	26.5(3.8)	26.2(3.6)	25.9(3.7)	25.6(3.6)	26.3(3.6)	26.6(4.1)	26.5(4.2)	26.2(3.7)
Activity, MET-h/week <sup>b</sup>	35.4(41.2)	32.9(39.7)	28.1(44.2)	19.2(29.0)	33.9(40.7)	28.7(42.6)	28.4(40.0)	30.2(35.3)
Regular aspirin use (2 or more tablets/wk), %	50	50	52	53	49	57	58	58
Past smoking, %	43	44	43	43	43	45	50	47
Current smoking, %	4	5	5	7	5	5	4	4
Multivitamin use <sup>c</sup> , %	70	67	64	56	66	71	78	78
Total energy intake, kcal/d	2072(638)	1980(615)	1925(606)	1880(614)	1995(619)	2043(658)	2012(643)	2019(628)
Alcohol, g/day	10.8(14.3)	11.0(13.9)	9.0(12.3)	8.9(13.6)	11.0(14.0)	10.1(13.4)	8.6(11.8)	10.3(13.8)
Total calcium intake <sup>d</sup> , µg/d	1066(515)	998(469)	966(430)	939(480)	1006(475)	1040(502)	1032(504)	1069(515)
Total folate intake <sup>d</sup> , µg/d	732(334)	697(323)	680(322)	629(313)	696(325)	724(328)	773(321)	766(332)
Total vitamin D <sup>d</sup> , IU/d	482(318)	455(306)	451(310)	410(320)	455(309)	474(315)	523(313)	510(314)
Total fiber <sup>d</sup> , g/d	24.5(7.7)	23.9(7.4)	23.4(7.2)	23.3(8.3)	23.8(7.4)	24.1(7.5)	24.8(7.3)	25.9(8.0)
Red meat, servings/wk	1.7(1.3)	1.7(1.2)	1.7(1.2)	1.7(1.4)	1.7(1.3)	1.7(1.2)	1.6(1.2)	1.6(1.1)
Processed meat, servings/wk	1.1(1.3)	1.1(1.3)	1.1(1.3)	1.2(1.5)	1.1(1.3)	1.1(1.2)	1.1(1.3)	1.0(1.2)
Bowel movement frequency every 3 days or less, %	NA				1	3	11	4
Laxative use weekly to daily, %	8	8	13	23	NA			

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

<sup>a</sup>Body mass index was calculated as weight in kilograms divided by the square of height in meters.

<sup>b</sup>MET denotes metabolic equivalent. MET-hours = sum of the average time/week spent in each activity x MET value of each activity.

<sup>c</sup>Dietary intakes were estimated with food-frequency questionnaire in 1998 except for multivitamin use from the 2000 questionnaire.

<sup>d</sup>Nutrient values were energy-adjusted intake.

\* Value is not age adjusted

Table 2

Multivariable relative risk\* of colorectal cancer according to frequency of bowel movement in the Nurses' Health Study (1982-2010) and in the Health Professionals Follow-up Study (2000-2010)

The Nurses' Health Study	Frequency of bowel movement			P for trend
	>1/day	daily	every 2 days or less	
<b>Colorectal cancer (n=1737)</b>	169	1155	294	119
	0.86 (0.73,1.01)	1.0 (Reference)	0.99 (0.87,1.13)	0.86 (0.71,1.04)
<b>Colon cancer (n=1374)</b>	140	892	251	91
	0.92 (0.77,1.11)	1.0 (Reference)	1.11 (0.96,1.27)	0.86 (0.69,1.07)
<b>Proximal colon cancer (n=822)</b>	86	536	142	58
	0.96 (0.76,1.21)	1.0 (Reference)	1.05 (0.87,1.26)	0.92 (0.70,1.21)
<b>Distal colon cancer (n=513)</b>	48	333	102	30
	0.82 (0.61,1.12)	1.0 (Reference)	1.20 (0.96,1.50)	0.74 (0.51,1.08)
<b>Rectal cancer (n=363)</b>	29	263	43	28
	0.63 (0.43,0.93)	1.0 (Reference)	0.62 (0.45,0.85)	0.86 (0.58,1.27)
The Health Professionals Follow-up Study	>1/day	daily	every 2 days or less	P for trend
<b>Colorectal cancer (n=275)</b>	67	192	16	16
	0.97 (0.73,1.29)	1.0 (Reference)	0.81 (0.48,1.37)	0.81 (0.48,1.37)
<b>Colon cancer (n=205)</b>	43	149	13	13
	0.79 (0.55,1.11)	1.0 (Reference)	0.84 (0.47,1.51)	0.84 (0.47,1.51)
<b>Proximal colon cancer (n=91)</b>	16	69	6	6
	0.70 (0.40,1.21)	1.0 (Reference)	0.77 (0.32,1.85)	0.77 (0.32,1.85)
<b>Distal colon cancer (n=72)</b>	19	48	5	5
	1.10 (0.63,1.92)	1.0 (Reference)	0.98 (0.38,2.58)	0.98 (0.38,2.58)
<b>Rectal cancer (n=70)</b>	24	43	3	3
	1.58 (0.92,2.70)	1.0 (Reference)	0.70 (0.21,2.35)	0.70 (0.21,2.35)

\* Adjusted for age (in months), smoking before age 30 (0, 1-4, 5-10, or >10 pack-years), history of colorectal cancer in a parent or sibling (yes, no), history of endoscopy (yes, no), regular aspirin use (yes, no), body mass index (<25, 25-30, 30 kg/m<sup>2</sup>), physical activity (<3, 3-27, 27 MET-hrs/wk), postmenopausal hormone use (premenopausal, never, past, or current user, women only), consumption of processed meat (quintiles), alcohol consumption (0-5, 5-10, 10-15, or 15 g/d), energy-adjusted total calcium intake (quintiles), total folate (quintiles), total fiber (quintiles), total vitamin D intake (quintiles), and total energy intake (quintiles).

Table 3

Multivariable relative risk\* of colorectal cancer according to frequency of laxative use in the Nurses' Health Study (1982-2010) and in the Health Professionals Follow-up Study (2000-2010)

	Frequency of laxative use			P for trend
	never	less than monthly	monthly, weekly-daily	
<b>The Nurses' Health Study</b>				
<b>Colorectal cancer (n=1737)</b>	1254	301	73	109
	1.0 (Reference)	0.97 (0.85,1.10)	0.94 (0.74,1.19)	0.98 (0.81,1.20)
<b>Colon cancer (n=1374)</b>	983	237	64	90
	1.0 (Reference)	0.97 (0.84,1.12)	1.03 (0.80,1.33)	1.04 (0.84,1.29)
<b>Proximal colon cancer (n=822)</b>	594	139	36	53
	1.0 (Reference)	0.94 (0.78,1.13)	0.96 (0.69,1.35)	1.00 (0.75,1.33)
<b>Distal colon cancer (n=513)</b>	363	94	25	31
	1.0 (Reference)	1.04 (0.82,1.30)	1.09 (0.72,1.63)	1.00 (0.69,1.44)
<b>Rectal cancer (n=363)</b>	271	64	9	19
	1.0 (Reference)	0.95 (0.73,1.26)	0.55 (0.28,1.08)	0.79 (0.49,1.26)
<b>The Health Professionals Follow-up Study</b>				
<b>Colorectal cancer (n=275)</b>	223	17	35	
	1.0 (Reference)	0.81 (0.48,1.37)	1.41 (0.96,2.06)	0.07
<b>Colon cancer (n=205)</b>	163	14	28	
	1.0 (Reference)	0.93 (0.52,1.67)	1.40 (0.91,2.15)	0.12
<b>Proximal colon cancer (n=91)</b>	70	8	13	
	1.0 (Reference)	1.10 (0.48,2.53)	1.34 (0.71,2.53)	0.38
<b>Distal colon cancer (n=72)</b>	61	2	9	
	1.0 (Reference)	0.38 (0.09,1.58)	1.10 (0.52,2.35)	0.71
<b>Rectal cancer (n=70)</b>	60	3	7	
	1.0 (Reference)	0.57 (0.16,2.00)	1.51 (0.65,3.52)	0.31

Covariates are the same as those listed in Table 2.

Table 4

Multivariable relative risk\* of colorectal cancer in relation to frequency of bowel movement or laxative use according to years of onset in the Nurses' Health Study

	Frequency of bowel movement				P for trend
	>1/day	daily	every 2 days	every 3 days or less	
Colorectal cancer onset within 10 years of assessment	42	301	66	30	
	0.77 (0.55,1.07)	1.0 (Reference)	0.90 (0.69,1.18)	0.87 (0.59,1.27)	0.52
Colorectal cancer onset 11-18 years after assessment	55	380	103	46	
	0.85 (0.64,1.13)	1.0 (Reference)	1.08 (0.86,1.34)	1.03 (0.85,1.26)	0.18
Colorectal cancer onset 19-28 years after assessment	72	474	125	43	
	0.92 (0.71,1.18)	1.0 (Reference)	0.99 (0.81,1.21)	0.73 (0.54,1.01)	0.69

  

	Frequency of laxative			P for trend	
	never	less than monthly	use monthly weekly-daily		
Colorectal cancer onset within 10 years of assessment	326	65	19	29	
	1.0 (Reference)	0.79 (0.60,1.03)	0.92 (0.57,1.46)	0.93 (0.63,1.37)	0.82
Colorectal cancer onset 11-18 years after assessment	406	117	23	38	
	1.0 (Reference)	1.15 (0.94,1.42)	0.93 (0.61,1.42)	1.03 (0.74,1.44)	0.91
Colorectal cancer onset 19-28 years after assessment	522	119	31	42	
	1.0 (Reference)	0.95 (0.78,1.16)	0.98 (0.68,1.41)	0.98 (0.71,1.35)	0.93

Covariates are the same as those listed in Table 2.