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A prospective study of bowel movement frequency, constipation, and laxative use on colorectal cancer risk

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Abstract

OBJECTIVE—Constipation and laxative use have been hypothesized to increase colorectal cancer (CRC) risk, but existing epidemiologic studies have been inconclusive. To address this issue, the authors prospectively examined the association between CRC incidence and constipation, non-fiber laxative use, and fiber laxative use among 75,214 participants of the VITamins And Lifestyle (VITAL) study.

DESIGN—Information on bowel movement frequency as well as average 10-year non-fiber laxative use, fiber laxative use, and constipation was ascertained by questionnaire. Persons were followed from the time baseline questionnaire was received (2000–2002) until 2008 for CRC incidence, over which time 558 incident CRC cases occurred. Cox proportional hazard models were used to estimate the multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CI).

RESULTS—Compared to individuals who used non-fiber laxatives less than once per year, the HRs associated with low (1–4 times per year) and high (> 5 times per year) use were 1.49 (95% CI: 1.04–2.14) and 1.43 (95% CI: 0.82–2.28), respectively, ($P_{\text{trend}} = 0.05$). HRs for CRC were statistically significantly decreased and lowest in individuals who reported using fiber laxatives often (4+ days per week for 4+ years) versus those who reported no use (HR = 0.44, 95% CI: 0.21–0.95), although the trend was not significant ($P_{\text{trend}} = 0.19$). No statistically significant associations between bowel movement frequency or constipation and colorectal cancer risk were observed.

CONCLUSIONS—Findings from this study suggest that risk of CRC increases with non-fiber laxative use and decreases with fiber laxative use. However, further observational and experimental studies are needed to clarify these relationships before drawing conclusions about the preferred treatment of constipation.

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COMPETING INTERESTS

None of the authors had a conflict of interest.

Keywords

Bowel habits; colorectal cancer; laxative use; prospective study

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common incident cancer in United States, with an estimated 142,820 new cases expected to occur in 2013¹. In the early 1970's, Burkitt and colleagues hypothesized that infrequent bowel movements increased colorectal cancer risk by increasing both the concentrations of carcinogens in the stool and the duration in which these carcinogens are in contact with the colonic mucosa². Multiple studies have attempted to address this topic, with a meta-analysis of case-control studies conducted in 1993³ and several later case-control studies^{4,5} reporting that infrequent bowel movements or constipation was associated with an increased risk of colorectal cancer. However, case-control studies are prone to bias as disease status may have influenced recall of actual or perceived bowel motility. Although several cohort studies have also reported a positive association between constipation and CRC^{6,7}, others have shown no association⁸⁻¹⁰, or even inverse associations^{6,11} between infrequent bowel movements and colorectal cancer risk. However, many of these studies were limited by small sample sizes and short follow-up periods. Additionally, results may have been further obfuscated by the complexity of characterizing bowel motility as well as the widespread use of laxatives.

Laxatives, utilized by roughly 20% of the U.S. population, have also been hypothesized to increase colon cancer risk. Stimulant purgatives, the most commonly used laxative, have been found to demonstrate mutagenic and carcinogenic effects in both *in vitro* and animal studies^{12,13}. However, prior cohort studies on laxative use^{6,11,14,15} have yielded inconsistent results, which may be due to a failure to account for differential risks by laxative subtype (stimulant, bulk [i.e. fiber], lubricant, and saline). Conversely, fiber laxative use might reduce CRC risk, as the World Cancer Research Fund-American Institute for Cancer Research (WCRF/AICR) second expert report¹⁶ suggests that there is convincing evidence that foods containing dietary fiber decrease colorectal cancer risk. However, no previous cohort studies have reported on the association between bulk (fiber) laxatives and CRC risk. Thus, to address these limitations of prior studies, we conducted a prospective study of bowel movement frequency, constipation, and laxative use by type (non-fiber vs. fiber) within the Vitamins and Lifestyle (VITAL) cohort.

METHODS

Study Population

As previously reported¹⁷, the VITAL study is a prospective study designed to investigate the association between vitamins, minerals, and other dietary supplements and cancer risk. Briefly, men and women aged 50 to 76 years at baseline who lived in the 13-county region in western Washington State covered by the Surveillance, Epidemiology, and End Results (SEER) cancer registry were eligible to participate. Between October 2000 and December 2002, baseline questionnaires were mailed to 364,418 individuals who were identified by a

commercial mailing list. Among these, 77,719 (21.3%) individuals returned questionnaires and satisfied eligibility requirements.

Exclusion criteria for these analyses included persons with: a history of CRC at baseline (n = 971) as well as those with missing baseline CRC information (n = 213), a history of ulcerative colitis or Crohn's disease (n = 1,030), intestinal polyposis (n = 273), diagnosis with *in situ* CRC over the period of follow-up (n = 12), cancer noted on death certificate only with no diagnosis date available (n = 1), and a diagnosis with CRC of certain rare morphologies (listed below, n = 33). Additionally, individuals who were missing information on all four exposure variables (n = 15) were excluded, leaving 75,214 persons for analyses. The above-listed exclusions are not mutually exclusive, so individuals may have been excluded for more than one reason. Study participants provided informed consent and study procedures were approved by the Fred Hutchinson Cancer Research Center Institutional Review Board.

Exposure Assessment

VITAL participants completed a self-administered, sex-specific, 24-page questionnaire on supplement use, medication use, health history, risk factors, and diet.

Closed-ended questions were used to ascertain 10-year average history of constipation (Over the past 10 years, how often did you feel constipated enough to take something, such as a laxative, enema or prunes?) and non-fiber laxative use (Over the past 10 years, about how many times have you taken non-fiber laxatives [such as Ex-lax, Correctol or milk of magnesia]?). Response options (never or less than once per year, 1–4 times per year, 5–11 times per year, 1–3 times per month, or 1 time per week or more) were then categorized into three groups by combining the last 3 categories. Bowel movement frequency, which was ascertained by asking participants a closed-ended question (How often do you usually have a bowel movement?), was combined into four categories (less than 5 times per week, 5–6 times per week, 1 time per day, and 2 or more times per day).

Fiber laxative use was ascertained by asking separate questions on frequency and duration of use of “fiber products such as Metamucil, Citrucel, FiberCon or Fiberall” in the 10-year period prior to baseline. Fiber laxative use was then categorized into three groups: high use (4+ days per week for 4+ years), low use (<4 days per week OR <4 years), or no use. These categories were created *a priori* so that the highest level of exposure is defined by high frequency (4+ days per week) and substantial duration (4+ years) of use.

Participants also reported on personal characteristics as part of the baseline questionnaire, including age, sex, ethnicity, education, height, weight, dietary intake, recreational physical activity, cigarette smoking, alcohol consumption, family history of cancer, and medical history. Dietary intakes were assessed using a semi-quantitative FFQ, adapted from instruments developed for the Women's Health Initiative (WHI) and other studies^{18–20}. Participants reported their usual frequency and portion size (small, medium, or large relative to a given portion size and to photographs of portion sizes) of 120 foods and beverages consumed during the year prior to baseline. Body mass index (BMI) was calculated from self-report of height and weight. Recreational physical activity was measured as average

total metabolic equivalent (MET) hours per week over the past 10 years, based on the reported years, frequency, and estimated energy expenditure for different moderate/vigorous activities.

Ascertainment of Case Status, Site and Stage

Cohort members were followed for incidence of colorectal cancer (ICD-3 18.0 – 20.9) from enrollment to December 31, 2008, by linking the study cohort to the western Washington Surveillance, Epidemiology and End Results (SEER) cancer registry. After excluding *in situ* cases, carcinoid tumors, neuroendocrine carcinomas and lymphomas, there were 558 eligible invasive cancers of the colon and rectum. Stage was based on SEER stage which defines localized cancer as cancer that is limited to the organ in which it began, regional as beyond the original site to nearby lymph nodes or organs and tissues, and distant as cancer that has spread to distant organs or distant lymph nodes. Colon cancer cases included those with ICD-O-3 codes of 18.0–18.9 and rectal cancer cases were those with ICD-O-3 codes of 19.9 and 20.9. Cases were followed until date of CRC diagnosis and non-cases were censored at whichever occurred earliest: date of death (6.7%), date of emigration out of the SEER catchment area (5.5%), date of requested removal from study (0.03%), or end of follow-up period, December 31st, 2008 (87.8%). Deaths occurring within the state of Washington were identified by linkage to the state death file, while emigrations out of area were identified by linkage to the National Change of Address System and by telephone calls and mailings.

Statistical Analysis

Logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (95% CI) to evaluate associations between baseline study participant characteristics and laxative use.

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs for the associations of bowel habits and laxative use with the risk of colorectal cancer. Age was the time metric in regression models, with participants entering at the age of completing the baseline questionnaire and exiting at their age at the end of follow-up. P for trend was modeled by treating the categorical exposure variable as continuous.

Covariates included in multivariate analyses were selected *a priori* and included factors associated with CRC. The multivariate model included the following covariates: age, sex, race/ethnicity, education, BMI (kg/m²), physical activity, smoking history, energy intake, total calcium intake, alcohol consumption, multivitamin use, dietary fiber intake, fruit/vegetable intake excluding potatoes, red/processed meat intake, hormone replacement therapy, as well as aspirin use and non-aspirin NSAID use. Analyses also included adjustment for family history of CRC among 1st degree relatives, history of sigmoidoscopy/colonoscopy in the 10 years prior to baseline, and history of polyp removal. Additionally, hazard ratios were estimated with models mutually-adjusted for all exposure variables (constipation, bowel movement frequency, fiber laxative use and non-fiber laxative use).

Stratified analyses were performed to examine the association between laxative use and CRC risk by sex. P-values for interaction by sex were calculated by including a single cross-

product term between laxative use, modeled as a continuous categorical variable, and sex in the unstratified, mutually-adjusted multivariate model.

We also evaluated heterogeneity of the laxative-CRC association by cancer site (colon vs. rectum), and cancer stage (local vs. regional/distal) at time of diagnosis. Logistic regression limited to cases was used to determine the statistical significance of subsite- and stage-specific differences. Additionally, a sensitivity analysis, which excluded all cases diagnosed within one year of follow-up, was performed to address the possibility that preclinical CRC may influence bowel habits and laxative use. The one-year follow-up period was selected as CRC diagnoses usually occur within one year of onset of symptoms^{21,22}.

All reported P-values are two-sided, and a P-value < 0.05 was considered statistically significant. All analyses were carried out using STATA 11 (StataCorp, College Station, TX).

RESULTS

Selected characteristics of VITAL participants as well as age- and sex- adjusted ORs and 95% CIs for the association between these characteristics and fiber and non-fiber laxative use are given in Table 1. Increasing age, female sex, history of colonoscopy, history of polyp removal, aspirin/NSAID use, and HRT use were positively associated with both fiber and non-fiber laxative use. Education, moderate/vigorous physical activity, dietary fiber intake, and fruit and vegetable consumption were positively associated with fiber laxative use and inversely associated with non-fiber laxative use. Alcohol consumption was less common in those who used non-fiber and fiber laxatives. Bowel movement frequency was inversely related to non-fiber laxative use. While constipation was positively associated with both fiber and non-fiber laxative use, the association was more pronounced for non-fiber laxative use.

Participants were followed for a total of 494,902 person-years. Cancer cases contributed 1,948 person-years while controls contributed 492,954 person-years.

Associations of bowel habits and laxative use with CRC risk are presented in Table 2. Constipation and bowel movement frequency were not statistically significantly associated with CRC risk in either the multivariate model adjusted for covariates or in the fully-adjusted model which included covariates as well as the four interrelated main exposures. Results for non-fiber and fiber laxative use were similar in the multivariate and fully-adjusted models. In the full, mutually-adjusted model, both low (1–4 times per year on average over the past 10 years) and high (≥ 5 times per year) non-fiber laxative use over the prior 10 years were associated with 43–49% increase in CRC risk relative to use less than once a year (HR = 1.49, 95% CI: 1.04–2.14; HR = 1.43, 95% CI: 0.82–2.48, respectively); although this is not a monotonic trend, there was a statistically significant trend across the three groups ($P_{\text{trend}} = 0.05$). High fiber laxative use over the past 10 years (≥ 4 days per week and ≥ 4 years) vs. none was associated with a statistically significant decrease in CRC risk (HR = 0.44, 95% CI: 0.21–0.95); however, there was no risk reduction for low fiber laxative

use (HR = 1.17, 95% CI: 0.82–1.68) and the test for trend was non-significant ($P_{\text{trend}} = 0.19$).

Tables 3, 4, and 5 present analyses of the findings related to the two types of laxative use stratified by sex, anatomic subsite, and cancer stage at diagnosis, respectively. The association between high non-fiber laxative use in the 10 years prior to baseline and increased cancer risk was more apparent for men than women, for colon cancer (vs. rectal) and for local (vs. regional/distant) CRC, although the differences were not statistically significant (all $P_{\text{interaction}} > 0.10$). The inverse association between fiber laxative use and CRC risk was similar for men and women, colon and rectum, and local and regional/distant disease, with no evident heterogeneity (all $P_{\text{interaction}} > 0.47$). Finally, the risk reduction associated with high fiber laxative use was similar among those in the lower half of dietary fiber intake (HR = 0.54, 95% CI: 0.20–1.47) and those in the upper half (HR = 0.36, 95% CI: 0.11–1.15; $P_{\text{interaction}} = 0.26$) (data not shown).

In a sensitivity analyses, the associations between bowel habit, laxative use, and colorectal cancer risk remained virtually unchanged after excluding cases diagnosed within one year of follow-up.

DISCUSSION

Results from this study do not provide evidence of an association between bowel movement frequency or constipation, and colorectal cancer risk. The association between laxative use and CRC risk varied by laxative type: use of non-fiber laxatives was associated with a significantly increased risk of colorectal cancer, whereas high use of fiber laxatives was associated with decreased risk. There was no evidence of differential effects by sex, cancer site, or cancer stage. However, the stratified results in Tables 3, 4, and 5 led to small numbers in some cells and limited power to detect main laxative effects within subgroups or to detect significant interactions.

Although a meta-analysis of case-control studies³ and several later case-control studies^{4,23–25} reported that infrequent bowel movements or increased constipation were positively associated with CRC risk, case-control studies are prone to selection and recall bias. Furthermore, the retrospective assessment of bowel habits in case-control studies is subject to issues of reverse causality, as changes in constipation frequency and bowel motility may be symptoms of colon cancer. Lastly, not many studies made mutual adjustment for bowel movement frequency and laxative use in their models despite the possibility that use of laxatives to treat constipation, rather than constipation itself, might potentially increase the risk of CRC. Consistent with these concerns, several cohort studies, including the Miyagi cohort study, the Nurses' Health Study, the Health Professionals Follow-Up Study, and the Japan Public Health Center Prospective Study^{6–9,14}, as well as conclusions from a systematic review on constipation, bowel-movement frequency, and CRC risk²⁶ have not found associations between bowel motility and CRC risk. However, contrary to our findings, the Japan Collaborative Cohort Study found infrequent bowel movement to be associated with increased risk (women reporting a bowel movement every 6 days or less vs. 1 per day, IRR = 2.47, 95% CI: 1.01–6.01)⁶ whereas the Netherlands

Cohort Study on Diet and Cancer reported that constipation and bowel movement infrequency were associated with decreased CRC risk (bowel movements every 2 days or less vs. 1 time per day – HR = 0.72, 95% CI: 0.52–1.01, $P_{\text{trend}} < 0.001$; constipation: sometimes or more often vs. never – HR = 0.76, 95% CI: 0.58–0.98, $P_{\text{trend}} = 0.02$)¹¹. Thus, although our findings do not support the hypothesis on bowel motility and CRC risk proposed by Burkitt, our null results are consistent with those observed in most cohort studies and the meta-analysis.

Although many previous cohort studies failed to find an association between laxative use and CRC risk^{8,15}, results may have been obscured by the fact that no distinction was made between stimulants and other laxatives. *In vitro* studies suggest that anthranoids, a type of stimulant laxative, have mutagenic and genotoxic effects, while animal studies have demonstrated that anthranoids increase cell proliferation activity¹³. Case-control studies examining stimulant laxatives have found that use was positively associated with CRC risk, including one by Siegers et al. (RR = 1.37; statistically non-significant) and another by Jacobs et al. (phenolphthalein laxatives: 350 lifetime uses vs. no regular use, OR = 3.9, 95% CI: 1.5–10.0)^{4,27}. Previous studies examining the association between laxative use of any type and CRC by sex have yielded mixed results, with some reporting no interaction^{7,23} and others reporting a statistically non-significant stronger association in women than in men^{23,28,29}, providing little support for our finding of an apparent stronger increased risk for non-fiber laxative use among men. However, there was no evidence of formal effect modification by sex in the current study.

Our fiber laxative results are similar to two previously published case-control studies: one which found that high fiber laxative use was inversely associated with CRC risk (fiber laxatives users vs. non-users, OR = 0.58, 95% CI: 0.32–1.05)²³ and another that found that all commercial laxatives, except fiber laxatives, appeared to be associated with increased CRC risk (fiber laxatives, 350 lifetime uses vs. no regular use, OR = 0.6, 95% CI: 0.2–2.1)⁴. In contrast, our findings are not consistent with two randomized controlled trials of fiber supplementation and colorectal adenoma recurrence, one of which found no effect of supplementation with a high wheat-bran-fiber cereal³⁰, and another which found an adverse effect on adenoma recurrence with supplementation of ispaghula husk³¹. However, experimental and observational data provide biologic evidence that a high dietary fiber intake is associated with decreased CRC risk by diluting carcinogens, binding carcinogenic secondary bile acids, and providing an important metabolic substrate (butyrate) to colonic cells as a result of bacterial fermentation³². Additionally, dietary fiber may reduce CRC by producing short chain fatty acids as well as normalizing cell proliferation and differentiation³³.

Given that we found CRC risk to be dependent upon laxative type, findings from the current study would help to explain the inconsistencies in previous studies that grouped all laxative types together. However, further research by laxative subtype is needed, as non-fiber laxatives encompass a broad range of agents which may be differentially associated with CRC risk.

Strengths of this study include the large cohort size, the essentially complete follow up, and the measurements of covariates, which allowed for adjustment of multiple CRC risk factors. Additionally, the prospective design of the study allowed data on bowel habit and laxative use to be collected prior to diagnosis of CRC, thus reducing bias resulting from reverse causality. Additionally, excluding cancer cases identified during the first year of follow up did not impact point estimates, a finding that supports the likelihood that reverse causality did not influence results. Lastly, our findings for laxative use and CRC by stage suggest that the associations were not stronger for those with more advanced stage, as would be expected if disease stage affected laxative use.

Study limitations include use of self-reported measures, which may have led to misclassification, as well as lack of detailed information on stool consistency. Previous studies have found that loose stools were related to an increased risk of colorectal cancer^{9,10}. As such, more specific measures of bowel function, such as stool weight and consistency, may provide additional information related to the effect of bowel function on colorectal cancer risk. In addition, as described in the results section above, our findings for both fiber laxative use and non-fiber laxative use did not show monotonic trends across none, low, and high use. While the associations between laxative use and CRC persisted after adjusting for covariates, findings may still be attributable to residual or unmeasured confounding and not due to casual associations. Furthermore, the stratified analyses of the associations between laxative use and CRC risk were limited in power, as case numbers in the highest exposure groups were small, and thus need replication.

In addition, confounding by indication is a concern in any epidemiologic study of drugs. Specifically, it is possible that more severe constipation was more likely treated by non-fiber laxatives, and it is the severe constipation rather than the non-fiber laxative use that led to the increased risk. However, constipation was not a risk factor for colorectal cancer in this study, and adjusting for constipation had little impact on the risk estimates associated with use of fiber or non-fiber laxatives. Furthermore, we found associations with colorectal cancer risk to be in opposite directions for fiber and non-fiber laxative use, even though both are associated with constipation. Nonetheless, it is difficult to separately define constipation and laxative use, and therefore difficult to have full confidence in whether the drug or its indication is driving the association.

In summary, we observed that non-fiber laxative use was associated with an increased risk of CRC whereas fiber laxative use was inversely associated with risk. However uncertainty remains about our findings due to lack of monotonic dose-response trends for our results, the possibility of residual confounding in observational epidemiologic studies, and lack of consistent support for our results from experimental studies, including one trial which found an adverse effect of supplemental fiber on adenoma recurrence³¹. Thus further research of specific laxative types is needed before conclusions can be drawn about recommending any specific type of laxative to patients with constipation.

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STUDY HIGHLIGHTS**What is already known about this subject?**

- Low bowel movement frequency and laxative use are suspected to increase colorectal cancer risk.
- However, previous epidemiologic studies examining bowel movement frequency, laxative use and CRC risk have yielded inconsistent results.

What are the new findings?

- High non-fiber laxative use was associated with an increased risk of colorectal cancer while fiber laxative use was associated with a decrease in CRC risk.
- No associations of bowel movement frequency or constipation with CRC were observed.

Table 1

Distribution of Colorectal Cancer (CRC) Risk Factors and Their Association with Laxative Use

	Cohort, N (%)	10 Year Non-Fiber Laxative Use OR (95% CI) ^a	10 Year Fiber Laxative Use OR (95% CI) ^b
Age at Baseline (yrs)			
50-<55	17,610 (23.4)	1.00	1.00
55-<60	17,124 (22.8)	1.13 (1.01–1.27)	1.36 (1.20–1.53)
60-<65	13,731 (18.3)	1.28 (1.14–1.44)	1.60 (1.41–1.80)
65-<70	12,347 (16.4)	1.51 (1.35–1.70)	2.12 (1.88–2.39)
70-<77	14,402 (19.2)	2.13 (1.92–2.37)	2.57 (2.30–2.87)
Sex			
Female	39,028 (51.9)	1.00	1.00
Male	36,186 (48.1)	0.30 (0.28–0.33)	0.89 (0.83–0.96)
Race/Ethnicity			
White	68,898 (93.2)	1.00	1.00
Hispanic	645 (0.87)	1.01 (0.69–1.49)	1.02 (0.69–1.50)
Black	956 (1.3)	2.55 (2.00–3.25)	0.72 (0.50–1.05)
American Indian/Alaska Native	1,100 (1.5)	1.24 (0.95–1.63)	1.01 (0.76–1.35)
Asian/Pacific Islander	1,869 (2.5)	0.76 (0.59–0.99)	0.64 (0.49–0.84)
Other	465 (0.6)	0.92 (0.56–1.50)	0.71 (0.41–1.21)
Education			
High School Graduate or Less	14,827 (20.1)	1.00	1.00
Some College or Tech Degree	28,281 (38.3)	0.81 (0.75–0.89)	1.08 (0.98–1.20)
College Graduate or Higher	30,837 (41.7)	0.52 (0.47–0.57)	1.28 (1.16–1.41)
Smoking			
Never	35,570 (47.7)	1.00	1.00
Former	32,774 (43.9)	1.35 (1.25–1.45)	1.14 (1.06–1.23)
Current	6,271 (8.4)	1.63 (1.44–1.83)	0.64 (0.55–0.75)
Body Mass Index (kg/m ²)			
Normal (<25)	25,006 (34.3)	1.00	1.00
Overweight (25 - <30)	29,984 (41.2)	0.96 (0.88–1.04)	0.95 (0.87–1.03)
Obese (30 - <35)	12,037 (16.5)	1.08 (0.97–1.20)	0.93 (0.83–1.03)
Severely Obese (35)	5,814 (8.0)	1.06 (0.93–1.21)	0.95 (0.82–1.09)
Physical Activity (MET/hr perweek mod/vig activity) c			
None	38,380 (51.7)	1.00	1.00
Tertile 1	12,007 (16.2)	0.88 (0.80–0.98)	1.11 (1.00–1.23)
Tertile 2	11,863 (16.0)	0.81 (0.73–0.90)	1.35 (1.22–1.49)
Tertile 3	11,930 (16.1)	0.82 (0.74–0.91)	1.35 (1.22–1.49)
Family History of CRC			
No	65,788 (88.6)	1.00	1.00
Yes	8,441 (11.4)	1.07 (0.97–1.19)	1.18 (1.07–1.31)
History of Colonoscopy/Sigmoidoscopy (Last 10 Yrs)			

	Cohort, N (%)	10 Year Non-Fiber Laxative Use OR (95% CI) ^a	10 Year Fiber Laxative Use OR (95% CI) ^b
No	32,709 (43.9)	1.00	1.00
Yes	41,866 (56.1)	1.56 (1.44–1.68)	3.20 (2.93–3.50)
History of Polyp Removal			
No	65,971 (87.7)	1.00	1.00
Yes	9,243 (12.3)	1.39 (1.27–1.53)	1.86 (1.70–2.02)
Aspirin Use			
No Use	40,225 (55.1)	1.00	1.00
Low Use (<4 days/week or <4 years)	17,133 (23.5)	1.31 (1.21–1.43)	1.31 (1.20–1.44)
High Use (4+ days/week and 4+ years)	15,712 (21.5)	1.62 (1.48–1.76)	2.09 (1.92–2.27)
NSAID Use (other than aspirin)			
No Use	51,408 (69.8)	1.00	1.00
Low Use(<4 days/week or <4 years)	17,145 (23.3)	1.59 (1.47–1.72)	1.70 (1.57–1.84)
High Use (4+ days/week and 4+ years)	5,108 (6.9)	2.37 (2.13–2.64)	2.22 (1.98–2.49)
Hormone Replacement Therapy Use (females)			
Never	13,152 (36.7)	1.00	1.00
Former	5,549 (15.5)	1.51 (1.37–1.66)	1.93 (1.72–2.17)
Current	17,116 (47.8)	1.64 (1.45–1.85)	1.62 (1.39–1.89)
Total energy intake (kcal/d)			
Q1 (<1282)	17,083 (25.0)	1.00	1.00
Q2 (1282 - < 1722)	17,082 (25.0)	0.80 (0.73–0.88)	0.96 (0.86–1.06)
Q3 (1722 - < 2287)	17,082 (25.0)	0.78 (0.70–0.86)	1.00 (0.90–1.12)
Q4 (2287 - < 4997)	17,082 (25.0)	0.83 (0.73–0.94)	1.04 (0.92–1.17)
Dietary Fiber Intake (g/day)			
Q1 (<12.5)	17,083 (25.0)	1.00	1.00
Q2 (12.5 - <17.5)	17,082 (25.0)	0.89 (0.81–0.98)	1.15 (1.02–1.29)
Q3 (17.5 - <23.7)	17,082 (25.0)	0.81 (0.73–0.90)	1.32 (1.18–1.48)
Q4 (23.7)	17,082 (25.0)	0.78 (0.69–0.87)	1.47 (1.31–1.65)
Fruit and Vegetable Intake - excluding potatoes (servings/d)			
Q1 (<2.1)	17,083 (25.0)	1.00	1.00
Q2 (2.1 - <3.2)	17,082 (25.0)	0.90 (0.81–1.00)	1.19 (1.06–1.34)
Q3 (3.2 - <4.8)	17,082 (25.0)	0.82 (0.74–0.92)	1.38 (1.23–1.55)
Q4 (4.8)	17,082 (25.0)	0.74 (0.66–0.82)	1.59 (1.42–1.78)
Red and Processed Meat Intake (oz./week) ^d			
Q1 (<9.2)	17,083 (25.0)	1.00	1.00
Q2 (9.2 - <17.1)	17,082 (25.0)	0.99 (0.90–1.10)	0.92 (0.83–1.02)
Q3 (17.1 - <28.3)	17,082 (25.0)	0.96 (0.86–1.06)	0.88 (0.79–0.99)
Q4 (28.3)	17,082 (25.0)	0.95 (0.84–1.07)	0.81 (0.72–0.90)
Alcoholic Drinks (Drinks)			
Q1 (<1/mo)	27,534 (37.6)	1.00	1.00
Q2 (1/mo - 4/week)	21,747 (29.7)	0.92 (0.85–1.00)	0.87 (0.80–0.95)
Q3 (> 4/week - < 2/day)	15,763 (21.5)	0.77 (0.69–0.85)	0.87 (0.79–0.96)

	Cohort, N (%)	10 Year Non-Fiber Laxative Use OR (95% CI) ^a	10 Year Fiber Laxative Use OR (95% CI) ^b
Q4 (2+ day)	8,279 (11.3)	0.73 (0.64–0.84)	0.87 (0.77–0.98)
Calcium (Diet + Supp) (mg/d)			
Q1 (<727)	16,969 (25.0)	1.00	1.00
Q2 (727 - < 1,039)	16,969 (25.0)	1.00 (0.90–1.12)	1.32 (1.16–1.49)
Q3 (1,039 - < 1,465)	16,969 (25.0)	0.87 (0.78–0.97)	1.58 (1.40–1.78)
Q4 (1,465)	16,969 (25.0)	0.99 (0.89–1.10)	2.13 (1.91–2.39)
Bowel Movement Frequency			
< 5x/week	7,478 (9.8)	6.04 (5.52–6.60)	1.24 (1.10–1.41)
5–6x/week	10,472 (13.7)	2.05 (1.85–2.26)	1.14 (1.02–1.27)
1x/day	36,451 (47.8)	1.00	1.00
2+ x/day	21,796 (28.6)	0.73 (0.66–0.81)	1.44 (1.33–1.56)
Constipation (10 year average)			
<1x/year	55,990 (74.1)	1.00	1.00
1–4x/year	11,146 (14.7)	28.03 (22.8–34.5)	2.03 (1.85–2.24)
>5x/year	8,479 (11.2)	331.9 (274.8–400.8)	5.41 (4.96–5.90)

^a Odds ratio (OR) for high use (≥ 5/y; n= 3,451) vs. low use (<1/y; n = 60,203) of non-fiber laxatives, adjusted for age and sex

^b OR for high use (≥ 2d/wk; n= 3,269) vs. low use (none; n = 64,113) of fiber laxatives, adjusted for age and sex

^c Tertiles of physical activity among those engaged in moderate/vigorous leisure physical activity determine within gender; women (T1: <2.81; T2: 2.81–9.45; T3: 9.45+); men (T1: <4.34; T2: 4.34–13.22; T3: 13.22+)

^d 1 oz = 28.35g

Hazard Ratios (HR) of Colorectal Cancer Associated with Bowel Habits and Laxative Use

Table 2

	Cases, n (%) ^a	Cohort, n (%) ^a	Age & Sex adjusted HR (95% CI)	Multivariate- adjusted HR ^b (95% CI)	Fully-adjusted HR ^c (95% CI)
Bowel Movement Frequency					
< 5x/week	55 (9.9)	7,368 (9.8)	1.12 (0.84–1.50)	1.09 (0.77–1.55)	1.06 (0.73–1.53)
5–6x/week	77 (13.8)	10,339 (13.8)	1.04 (0.81–1.34)	1.16 (0.87–1.54)	1.07 (0.79–1.45)
1x/day	274 (49.1)	36,058 (48.1)	1.00	1.00	1.00
2+ x/day	152 (27.2)	21,210 (28.3)	0.98 (0.81–1.20)	0.92 (0.73–1.16)	0.91 (0.72–1.16)
P _{trend}			0.40	0.18	0.36
Constipation (10 year average)					
<1x/year	388 (70.3)	55,119 (74.1)	1.00	1.00	1.00
1–4x/year	101 (18.3)	10,974 (14.6)	1.20 (0.96–1.50)	1.24 (0.96–1.61)	0.99 (0.72–1.37)
>5x/year	63 (11.4)	8,289 (11.1)	0.98 (0.75–1.29)	1.12 (0.81–1.56)	0.91 (0.59–1.41)
P _{trend}			0.61	0.21	0.73
Non-Fiber Laxative Use (10 year)					
<1x/year	413 (81.5)	60,203 (86.2)	1.00	1.00	1.00
1–4x/year	68 (13.4)	6,124 (8.8)	1.50 (1.16–1.94)	1.49 (1.10–2.02)	1.49 (1.04–2.14)
5x/year	26 (5.1)	3,451 (5.0)	1.05 (0.70–1.56)	1.36 (0.87–2.13)	1.43 (0.82–2.48)
P _{trend}			0.08	0.02	0.05
Fiber Laxative Use (10 year)					
Non-User	486 (89.8)	64,113 (87.1)	1.00	1.00	1.00
Low (<4 days/week or <4 yrs)	44 (8.1)	6,247 (8.5)	0.86 (0.63–1.17)	1.22 (0.87–1.71)	1.17 (0.82–1.68)
High (4+ days/week for 4+ yrs)	11 (2.0)	3,269 (4.4)	0.37 (0.21–0.68)	0.47 (0.23–0.95)	0.44 (0.21–0.95)
P _{trend}			0.001	0.26	0.19

^a n: # after fter adjustment for age and sex^b Adjusted for: age, sex, race/ethnicity, BMI, physical activity, education, fiber, calcium, fruit & vegetable intake, red/processed meat intake, alcohol consumption, smoking, NSAID use, aspirin use, family history of CRC, colonoscopy/sigmoidoscopy screening, history of polyp removal, hormone replacement therapy use (among women), and caloric intake^c Adjusted for: age, sex, race/ethnicity, BMI, physical activity, education, fiber, calcium, fruit & vegetable intake, red/processed meat intake, alcohol consumption, smoking, NSAID use, aspirin use, family history of CRC, colonoscopy/sigmoidoscopy screening, history of polyp removal, hormone replacement therapy use (among women), and caloric intake, laxative use, fiber laxative use, bowel movement frequency and constipation

Table 3

Hazard Ratios (HR) of Colorectal Cancer Associated with Laxative Use, by Sex

	Men		Women		P for interaction		
	Case/Cohort ^a	HR ^b (95% CI)	Case/Cohort ^a	HR ^b (95% CI)			
Non-Fiber Laxative Use (10 year)							
<1x/year	230/30,156	1.00	Ref	183/30,047	1.00	Ref	0.52
1–4x/year	19/2,103	1.10	(0.60–2.01)	49/4,021	1.84	(1.16–2.93)	
5x/year	9/806	2.34	(0.96–5.66)	17/2,645	1.14	(0.57–2.31)	
<i>P_{trend}</i>			0.13			0.18	
Fiber Laxative Use (10 year)							
Non-User	248/31,178	1.00	Ref	238/32,935	1.00	Ref	0.48
Low (<4 days/week or <4 yrs)	17/2,356	1.19	(0.69–2.05)	27/3,891	1.14	(0.70–1.86)	
High (4+ days/week for 4+ yrs)	6/1,504	0.41	(0.13–1.30)	5/1,765	0.48	(0.18–1.31)	
<i>P_{trend}</i>			0.33			0.39	

^a n: # after fier adjustment for all covariates (listed below)^b Adjusted for: age, sex, race/ethnicity, education, smoking, BMI, physical activity, family history of CRC, colonoscopy/sigmoidoscopy screening, history of polyp removal, aspirin use, NSAID use, hormone replacement therapy use (among women), caloric intake, fiber, fruit & vegetable intake, red/processed meat intake, alcohol consumption, calcium, non-fiber laxative use, fiber laxative use, bowel movement frequency and constipation

Table 4
Hazard Ratios (HR) of Colorectal Cancer Associated with Laxative Use, by Subsite

	Colon Cancer			Rectal Cancer		
	Case/Cohort ^a	HR ^b	(95% CI)	Case/Cohort ^a	HR ^b	(95% CI)
Non-Fiber Laxative Use (10 year)						
<1x/year	232/49,323	1.00	Ref	93/49,706	1.00	Ref
1–4x/year	44/4,719	1.60	(1.08–2.38)	6/4,753	0.98	(0.39–2.49)
5x/year	18/2,542	1.63	(0.89–2.98)	3/2,565	0.80	(0.20–3.09)
<i>P_{trend}</i>			0.002			0.78
Fiber Laxative Use (10 year)						
Non-User	274/52,039	1.00	Ref	99/52,039	1.00	Ref
Low (<4 days/week or <4 yrs)	31/5,049	1.22	(0.83–1.83)	8/5,049	0.91	(0.39–2.16)
High (4+ days/week for 4+ yrs)	6/2,681	0.40	(0.17–0.99)	2/2,681	0.57	(0.14–2.36)
<i>P_{trend}</i>			0.26			0.46

^a n: # after fier adjustment for all covariates (listed below)

^b Adjusted for: age, sex, race/ethnicity, education, smoking, BMI, physical activity, family history of CRC, colonoscopy/sigmoidoscopy screening, history of polyp removal, aspirin use, NSAID use, hormone replacement therapy use (among women), caloric intake, fiber, fruit & vegetable intake, red/processed meat intake, alcohol consumption, calcium, non-fiber laxative use, fiber laxative use, bowel movement frequency and constipation

Table 5

Hazard Ratios (HR) of Colorectal Cancer Associated with Laxative Use, by Stage

	Local		Regional/Distant		P for difference	
	Case/Cohort ^a	HR ^b (95% CI)	Case/Cohort ^a	HR ^b (95% CI)		
Non-Fiber Laxative Use (10 year)						
<1x/year	148/49,528	1.00	Ref	173/49,553	1.00	0.11
1–4x/year	20/4,723	1.46 (0.83–2.56)		30/4,733	1.53 (0.95–2.45)	
5x/year	10/2,554	1.85 (0.81–4.22)		11/2,555	1.17 (0.56–2.47)	
<i>P_{trend}</i>		0.08			0.25	
Fiber Laxative Use (10 year)						
Non-User	165/51,831	1.00	Ref	203/51,869	1.00	0.97
Low (<4 days/week or <4 yrs)	17/5,027	1.17 (0.70–1.95)		22/5,032	1.17 (0.73–1.93)	
High (4+ days/week for 4+ yrs)	4/2,677	0.41 (0.13–1.32)		4/2,677	0.48 (0.18–1.32)	
<i>P_{trend}</i>		0.34			0.39	

^a n: # after fier adjustment for all covariates (listed below)^b Adjusted for: age, sex, race/ethnicity, education, smoking, BMI, physical activity, family history of CRC, colonoscopy/sigmoidoscopy screening, history of polyp removal, aspirin use, NSAID use, hormone replacement therapy use (among women), caloric intake, fiber, fruit & vegetable intake, red/processed meat intake, alcohol consumption, calcium, non-fiber laxative use, fiber laxative use, bowel movement frequency and constipation