Published in final edited form as:

Ann Epidemiol. 2018 October ; 28(10): 739–741. doi:10.1016/j.annepidem.2018.06.011.

Laxative Type In Relation To Colorectal Cancer Risk

Jessica S Citronberg^{1,2}, Sheetal Hardikar^{3,4}, Amanda Phipps^{1,2}, Jane C. Figueiredo⁵, and Polly Newcomb^{1,2}

¹Department of Epidemiology, University of Washington, Seattle, WA

²Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA

³School of Medicine, University of Utah, Salt Lake City, UT

⁴Population Health Sciences, Huntsman Cancer Institute, Salt Lake City, UT

⁵Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles CA

Abstract

PURPOSE —Existing studies on laxatives, utilized by roughly 40% of the U.S. population experiencing constipation, and colorectal cancer (CRC) have yielded inconsistent results, which may be due to a failure to account for differential risks by major laxative types: bulk (fiber-based), and non-bulk (or non-fiber-based).

METHODS —We examined the association of non-fiber-based laxative use and fiber-based laxative use with the risk of CRC in a subset of the multi-site, international Colon Cancer Family Registry cohort comprised of 4,930 primary invasive colorectal cancer cases and 4,025 controls selected from the general population. Epidemiologic risk factor questionnaires were administered to all participants at recruitment and exposures were ascertained approximately one year prior to diagnosis for cases and at a comparable time period for controls. We ascertained known and suspected CRC risk factors, including regular laxative use, which was defined as laxative intake at least twice a week for more than a month. Multivariable logistic regression models were used to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (95% CI).

RESULTS —Individuals who reported using non-fiber-based laxatives regularly were at a significantly increased risk for CRC compared to those who reported no laxative use (OR = 2.17, 95% CI = 1.47-3.19). No statistically significant associations were observed between fiber-based laxative use and CRC (OR = 0.99, 95% CI = 0.80-1.22).

Corresponding Author: Jessica Citronberg, Fred Hutchinson Cancer Research Center, PO Box 19024, M4-B402, Seattle, WA 98102 (Phone: 206-667-4068, jcitronb@fredhutch.org).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of interest:

The authors acknowledge they have no conflicts of interest.

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Colon Cancer Family Registry (CCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government, any cancer registry, or the CCFR.

CONCLUSIONS —Compared to non-users, the risk of CRC increased with non-fiber-based laxative use, while CRC risk was not significantly associated with fiber-based laxative use.

Keywords

laxative use; colorectal cancer

Introduction:

Colorectal cancer (CRC) is the fourth most common incident cancer in the United States, with an estimated 135,430 new cases expected to occur in 2017 [1]. Laxatives, utilized by roughly 40% of the U.S. population experiencing constipation [2], have also been hypothesized to increase colorectal 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 [3,4]. Recently, phenolphthalein, the active ingredient in many stimulant laxative brands, has been shown to be associated with several different tumors, although not CRC [5]. Alternatively, fiber laxatives might be expected to reduce colon cancer risk as dietary fiber has been suggested to reduce CRC risk [6]. However, prior cohort studies on laxative use [7,8] 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).

Thus, the goal of this study was to examine the association between non-fiber-based laxative use, fiber-based laxative use, and the risk of CRC in the Colon Cancer Family Registry.

Methods:

Study Population and Overview

The Colon Cancer Family Registry (Colon CFR) is an international consortium of centers in North America and Australia formed as a resource to support studies on the etiology, prevention, and clinical management of colorectal cancer. Details of the registry enrollment protocols and eligibility criteria have been published [9] and are available at <http://coloncfr.org>. Briefly, cases were diagnosed between 1997 and 2008 with incident invasive adenocarcinoma of the colon or rectum and were aged 18 to 74 years. Epidemiologic and demographic information was collected using standardized questionnaires, although the mode of administration varied by site, and included in-person interviews, telephone interviews, and mailed questionnaires. The current study was restricted to CRC cases who were identified from population-based cancer registries and were recruited through three CCFR study centers (Fred Hutchinson Cancer Research Center, Seattle, WA; Cancer Care Ontario, Toronto, ON, Canada; and University of Melbourne, Melbourne, VIC, Australia). Controls were free of cancer and were recruited from the general population through medicare, drivers license files, telephone subscriber lists, and electoral rolls.

Individuals with a history of ulcerative colitis (n=222), Crohn's disease (n=99), and familial adenomatous polyposis (n=71) were excluded, leaving 8,955 participants (4,930 cases, 4,025 controls) in the primary analysis.

Questionnaires were used to collect self-reported information on demographics as well as known and suspected CRC risk factors including: age, sex, medication use (including NSAIDs, aspirin, vitamins, minerals, laxatives, and hormone therapy [for women] [ever and about 2 years prior to baseline]), family history of colorectal cancer, and history of digestive diseases (colitis, Crohn's disease, irritable bowel syndrome, or diverticulitis).

Laxative use was categorized into two types: fiber laxative and non-fiber laxative use. Regular use was ascertained by yes/no responses to questions on fiber laxative ("Have you ever taken bulk-forming laxatives [such as Metamucil, Citrucel, Fibercon, Serutan, and psyllium] at least twice a week for a month or longer?") and non-fiber laxative ("Have you ever taken other laxatives [such as Ex-Lax, Correctol, Dulcolax, Senokot, Colace, castor oil, cod liver oil, mineral oil, milk of magnesia, lactulose, Epsom salts] at least twice a week for a month or longer?") use.

Statistical Analysis

In separate models, we evaluated the associations for fiber- and non-fiber laxatives and risk of CRC using logistic regression models to estimate the crude and multivariable adjusted odds ratios (ORs) and 95% confidence intervals (95% CI). Covariates included in multivariable analyses were selected *a priori*, and included factors associated with either laxative use or CRC risk [6]. The multivariable model included the following covariates evaluated at baseline: age, sex, regular NSAID use 2 years prior, regular aspirin use 2 years prior, postmenopausal hormone therapy (HT) use (among women), study center site, and family history of CRC.

Stratified analyses were performed to examine the association between laxative use and CRC risk by sex and age, with age dichotomized at the median values of controls. P-values for interaction were calculated by including a single cross-product term between laxative use and the binary variable (male/female, age $\leq$ 60 years/age $>$ 60 years) in a single model, adjusted for the covariates listed above. A sensitivity analysis was also conducted excluding individuals who took both types of laxatives (11 controls, 25 cases), as these individuals may weaken an observed association between specific laxative type and CRC.

All reported *P*-values are two-sided, and a *P*-value $<$ 0.05 was considered statistically significant. All analyses were carried out using STATA 14 (StataCorp, College Station, TX).

Results:

The distribution of laxative use by case-control status and associations of laxative use with CRC risk are presented in Table 1. Fiber-based laxative use was slightly more common among controls (4.7%), (vs. 4.1% in cases) while non-fiber-based laxatives were more common among cases (1.9% vs. 1.0% in controls). In multivariable models comparing laxative users to non users, non-fiber laxative use was associated with a statistically significant increase in CRC risk (OR = 2.17, 95% CI: 1.47-3.19), while fiber laxative use was not associated with CRC risk (OR = 0.99, 95% CI: 0.80-1.22). There was no evidence of interaction between fiber laxative use and sex. While non-fiber laxative use was associated with a higher CRC risk in males (OR = 3.13, 95% CI: 1.23-7.93) compared to

females (OR = 1.97, 95% CI: 1.28-3.02) this difference was not statistically significant ($P_{\text{interaction}} = 0.37$).

In analyses limited to single type users only, the association was strengthened after excluding individuals who took both fiber and non-fiber laxatives (n=36) (fiber laxative: OR = 0.93, 95% CI: 0.75-1.17; Non-fiber laxative: OR = 2.19, 95% CI: 1.39-3.45).

Discussion:

In this study, non-fiber laxative use was statistically significantly associated with an over two-fold increase in CRC risk while fiber laxative use not was associated with CRC risk. Additionally, the association was strengthened by excluding individuals who took both fiber and non-fiber laxatives regularly. There was no evidence of interaction with sex or age for either type of laxative.

Results on non-fiber laxatives were in agreement with previous studies which measured non-fiber laxative use and CRC [10,11]. Additionally, *in vitro* studies suggest that anthranoid laxatives, a non-fiber compound, have mutagenic and genotoxic effects, and animal studies have demonstrated that anthranoids increase cell proliferation activity [3]. Another non-fiber laxative, phenolphthalein, has also been found to have a genotoxic effect and may cause oxidative damage in experimental and *in vitro* models [5,12]. However, our findings were not consistent with several case-control studies on anthranoids and phenolphthalein laxative use and CRC [13,14]. These case-control studies, which failed to find an association between non-fiber laxative use and CRC, used a small study population size, which may have limited the ability to detect potential associations between non-fiber laxatives and CRC. Additionally, differences in findings may be due to varying types of non-fiber laxatives included in each respective study.

Strengths of this study included the large number of CRC subjects with detailed epidemiologic assessments of their demographic and risk factor background according to standardized protocols.

Study limitations include use of retrospective design, which can lead to issues with reverse causality and recall bias. However, while the case control design may be susceptible to issues with temporality, laxative use in the current study was assessed for a time period before CRC may have been symptomatic, as a previous study suggests that the median duration of symptoms (from initial symptom onset to diagnosis) was 14 weeks (interquartile range 5–43 weeks) [15]. As such, given that CRC typically becomes symptomatic within 6 months prior to diagnosis, ascertainment of laxative use 1 year prior to diagnosis, the likelihood that preclinical CRC influenced bowel habits and subsequent laxative use in the current study is reduced. Nonetheless, given the study design, results may have been influenced by recall bias, with cases (or controls) incorrectly remembering laxative use prior to cancer diagnosis. Furthermore, failure to control sufficiently for potentially confounding variables, such as constipation and bowel movement frequency, may have led to biased point estimates. As such, large prospective cohort studies with detailed information on laxative use habits and lifestyle factors are needed to verify results.

In summary, we found that non-fiber laxative use was associated with a statistically significant increase in CRC risk, while fiber laxative use not was associated with CRC risk. Furthermore, this association was strengthened after excluding individuals who took both fiber and non-fiber laxatives regularly, supporting the results that laxative use is differentially associated with CRC risk, depending on laxative type. Thus, the observed differential risk by laxative subtype in the current study highlights the need to assess laxative type as separate exposures in future studies. Additionally, given the potential for bias inherent in the case control design, future prospective studies with information of specific laxative type are needed to validate findings.

Acknowledgements:

Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under Award Number UM1CA167551 and through cooperative agreements with the following CCFR centers: Australasian Colorectal Cancer Family Registry (NCI/NIH U01 CA074778 and U01/U24 CA097735), Ontario Familial Colorectal Cancer Registry (NCI/NIH U01/U24 CA074783) and Seattle Colorectal Cancer Family Registry (NCI/NIH U01/U24 CA074794). Support for case ascertainment was also provided from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute to Fred Hutchinson Cancer Research Center (Control Nos. N01-CN-67009 and N01-PC-35142, and Contract No. HHSN2612013000121) and by the Victorian Cancer Registry (Australia), and the Ontario Cancer Registry (Canada). Additional support was provided by NIH grants R25 CA094880 (to EM), and K05 CA152715 (to PAN).

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016 CA. *Cancer J. Clin.* [Internet]. [cited 2016 Jun 27];66:7–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/26742998> [PubMed: 26742998]
2. Wald A, Scarpignato C, Mueller-Lissner S, Kamm M, Hinkel U, Helfrich I, et al. A multinational survey of prevalence and patterns of laxative use among adults with self-defined constipation. *Aliment. Pharmacol. Ther* [Internet]. Blackwell Publishing Ltd; 2008 [cited 2017 Dec 5];28:917–30. Available from: <http://doi.wiley.com/10.1111/j.1365-2036.2008.03806.x> [PubMed: 18644012]
3. Van Gorkom BAP, De Vries EGE, Karrenbeld, Kleibeuker. Review article: anthranoid laxatives and their potential carcinogenic effects. *Aliment. Pharmacol. Ther* [Internet]. Blackwell Science Ltd; 1999 [cited 2017 Mar 15];13:443–52. Available from: <http://doi.wiley.com/10.1046/j.1365-2036.1999.00468.x> [PubMed: 10215727]
4. Koskela E, Kulju T, Collan Y, Mariani P, Villanacci V, Salerni B. Melanosis coli. Prevalence, distribution, and histologic features in 200 consecutive autopsies at Kuopio University Central Hospital. *Dis. Colon Rectum* [Internet]. American Association for Cancer Research; 1989 [cited 2017 Mar 15];32:235–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/2920631> [PubMed: 2920631]
5. Dunnick JK, Hailey JR. Phenolphthalein exposure causes multiple carcinogenic effects in experimental model systems. *Cancer Res.* [Internet]. American Association for Cancer Research; 1996 [cited 2017 Mar 15];56:4922–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8895745> [PubMed: 8895745]
6. Wiseman M The Second World Cancer Research Fund/American Institute for Cancer Research Expert Report. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. *Proc. Nutr. Soc* [Internet] 2008 [cited 2017 Jul 25];67:253–6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18452640> [PubMed: 18452640]
7. 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* [Internet] 2004 [cited 2017 Mar 15];40:2109–15. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0959804904005064> [PubMed: 15341986]
8. 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*

- [Internet] 2000 [cited 2017 Jul 25];151:958–64. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10853634> [PubMed: 10853634]
9. Newcomb PA, Baron J, Cotterchio M, Gallinger S, Grove J, Haile R, et al. Colon Cancer Family Registry: An International Resource for Studies of the Genetic Epidemiology of Colon Cancer. *Cancer Epidemiol. Biomarkers Prev.* [Internet] 2007 [cited 2017 Mar 17];16:2331–43. Available from: <http://cebp.aacrjournals.org/cgi/doi/10.1158/1055-9965.EPI-07-0648> [PubMed: 17982118]
10. Siegers CP. Anthranoid laxatives and colorectal cancer. *Trends Pharmacol. Sci.* [Internet] 1992 [cited 2017 Jul 25];13:229–31. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/1631961> [PubMed: 1631961]
11. Citronberg J, Kantor ED, Potter JD, White E. A prospective study of the effect of bowel movement frequency, constipation, and laxative use on colorectal cancer risk. *Am. J. Gastroenterol Nature Publishing Group*; 2014;109:1640–9. [PubMed: 25223576]
12. Sipe HJ, Corbett JT, Mason RP. In vitro free radical metabolism of phenolphthalein by peroxidases. *Drug Metab. Dispos.* [Internet] 1997 [cited 2017 Jul 25];25:468–80. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9107547> [PubMed: 9107547]
13. Nusko G, Schneider B, Schneider I, Wittekind Ch, Hahn E Anthranoid laxative use is not a risk factor for colorectal neoplasia: results of a prospective case control study. *Gut* [Internet] 2000 [cited 2017 Mar 15];46:651–5. Available from: <http://gut.bmj.com/cgi/doi/10.1136/gut.46.5.651> [PubMed: 10764708]
14. Coogan PF, Rosenberg L, Palmer JR, Strom BL, Zauber AG, Stolley PD, et al. Phenolphthalein Laxatives and Risk of Cancer. *J. Natl. Cancer Inst.* [Internet]. Oxford University Press; 2000 [cited 2017 Mar 15];92:1943–4. Available from: <https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/92.23.1943> [PubMed: 11106687]
15. Majumdar SR, Fletcher RH, Evans AT. How does colorectal cancer present? symptoms, duration, and clues to location. *Am. J. Gastroenterol* [Internet]. Nature Publishing Group; 1999 [cited 2017 Mar 15];94:3039–45. Available from: <http://www.nature.com/doi/10.1111/j.1572-0241.1999.01454.x> [PubMed: 10520866]

Table 1.

Estimated Odds Ratios (OR) of Colorectal Cancer Associated with Laxative Use

	Cases n (%)	Controls n (%)	Age & Sex Adjusted OR (95% CI)	Multivariate-Adjusted OR* (95% CI)	P-interaction
Non-Fiber Laxative Use					
Never	4,797 (98.1%)	3,970 (99.0%)	1	1	
Ever	94 (1.9%)	39 (1.0%)	2.15 (1.47-3.14)	2.17 (1.47-3.19)	
By Sex					
Male	22 (1.0%)	6 (0.3%)		3.13 (1.23-7.93)	0.37
Female	72 (3.0%)	33 (1.7%)		1.97 (1.28-3.02)	
By Age					
Age ≤ 60				1.96 (1.12-3.44)	0.69
Age > 60				2.35 (1.38-4.02)	
Fiber Laxative Use					
Never	4,692 (95.9%)	3,814 (95.3%)	1	1	
Ever	198 (4.1%)	190 (4.7%)	0.94 (0.76-1.15)	0.99 (0.80-1.22)	
By Sex					
Male	83 (3.4%)	75 (3.9%)		1.08 (0.78-1.51)	0.55
Female	115 (4.7%)	115 (5.6%)		0.94 (0.72-1.23)	
By Age					
Age ≤ 60	88 (2.8%)	67 (3.2%)		0.94 (0.67-1.31)	0.94
Age > 60	110 (6.3%)	123 (6.4%)		1.04 (0.79-1.37)	

* Adjusted for: age, sex, regular NSAID use 2 years prior, regular aspirin use 2 years prior, HT use (among women), center site, and family history of CRC