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Is bowel habit linked to colorectal cancer? – Results from the EPIC-Norfolk study

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ABSTRACT

Bowel habit has been associated with colorectal carcinogenesis; however, findings from epidemiologic studies have been limited and inconsistent. The aim of this study was to explore the association between bowel habit and colorectal cancer (CRC) risk in the UK-Norfolk arm of the European Prospective Investigation Into Cancer and Nutrition (EPIC-Norfolk), a study of 25,663 men and women aged 45–79 years at entry. Having loose stools compared to soft stools was associated with an approximately 3-fold increased risk, and the association remained significant when lifestyle factors and bowel habit variables were included as covariates in the model (odds ratio (OR), 2.80; 95% confidence interval (CI), 1.41–5.56). The significantly elevated risk estimate persisted when we further excluded CRC cases within 3 years of follow-up. Frequency of bowel movement, stool quantity, feeling discomfort and laxative use was not overall associated with CRC risk. These findings suggest that having loose stools may be an indicator of colorectal cancer risk.

1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide after lung and breast cancer in 2002 and the second most common incident form of cancer in Europe in 2004 (376,400 cases, 13% of all incident cases).[1,2] Around 100 new cases of CRC are diagnosed each day in the United Kingdom (UK) in 2006, being the second most common cause of death from cancer in the country.[3]

Constipation and infrequent bowel movement have long been suggested to be risk factors for colorectal cancer (CRC). In the early 1970s, Burkitt and colleagues hypothesised that bowel flora convert bowel contents to carcinogens or co-carcinogens by a time-dependent process.[4,5] They suggested that low bowel movement frequency from low fibre intake slows intestinal transit thereby prolonging mucosal contact with putative carcinogens in the colonic lumen. However, only a few studies have examined this hypothesis in relation to CRC risk despite its biological plausibility, and prospective studies investigating bowel habit are particularly sparse.

In 1993, a meta-analysis summarised results of nine published case-control studies examining bowel habit and demonstrated a statistically significant increased risk of CRC with constipation or infrequent bowel movement (odds ratio (OR), 1.48; 95% confidence interval (CI), 1.32–1.66).[6] However, the individual case-control studies were relatively

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inconsistent in defining constipation or infrequent bowel movement. In addition, two recent large prospective studies which showed null or negative associations between infrequent bowel movement and the risk of CRC do not agree with the finding from the meta-analysis.[7,8]

Conversely, it has also been postulated that intestinal hurry may be a risk factor for CRC having an irritant action on the mucosa of the large bowel, resulting in hyperplasia, dysplasia and neoplasia.[9] To date, however, only three case-control studies[10–12] and two prospective studies[8,13] assessed this hypothesis and provided equivocal evidence on the association of loose stools or frequent bowel movement and CRC risk.

Studies often fail to support an association between laxative use and CRC risk[7,12,14,15] although commercial laxative use is widely spread, and the uncontrolled long-term abuse of self-administered laxatives may have a harmful effect and may therefore cause several health problems.[16]

Overall, previous epidemiologic studies, mostly case-control studies, which examined bowel habit in relation to the development of CRC thus far have failed to support conclusively any of the proposed hypotheses. One of the possible explanations of these discrepancies may be that constipation and diarrhoea are common symptoms of CRC, and the relevant time period when risk factors act in the process of cancer development is often unknown.[7]

The aim of this nested case-control study was to investigate the prospective association between bowel habit, including bowel movement frequency, consistency, quantity, feeling of discomfort during bowel movement, laxative use and risk of CRC in participants of the UK-Norfolk cohort of the European Prospective Investigation Into Cancer and Nutrition (EPIC-Norfolk) study.

2. Materials and methods

2.1. Study population

The EPIC-Norfolk Study is an ongoing prospective study of 25,663 men and women aged between 45 and 79 years who were residing in Norfolk, United Kingdom, and were recruited from general practice registers. The design and study methods have been described previously.[17] The study was approved by the Norwich Ethics Committee, and participants gave signed informed consent.

2.2. Case ascertainment and control selection

Incident CRC cases (International Statistical Classification of Diseases and Related Health Problems (ICD) 9th revision, 153.0–153.9, 154.0 and 154.1) were ascertained by matching all participants to the East Anglian Cancer Registry and the United Kingdom Office for National Statistics, which provided notification of all cancer registrations, deaths and emigrations for the cohort. During an average of 12 years follow-up from the first health check, 299 cases were identified. For each case, four controls matched for age, sex and time of enrolment were selected from among participants who were free of cancer, except for non-melanoma skin cancer, at baseline. However, information about bowel movement frequency, the primary exposure of interest, was only available for 159 cases and 771 controls who completed a Follow-up Health Questionnaire. All analyses were restricted to these participants.

2.3. Assessment of bowel habit and covariates

Between 1993 and 1997, all participants completed a detailed health and lifestyle questionnaire, which included questions on smoking history, use of hormone replacement therapy (HRT) in women and physical activity. Participants were also sent a 130 food item Food Frequency Questionnaire (FFQ). For each food item, participants were asked to indicate their usual consumption, choosing from nine frequency categories. The categories ranged from 'never or less than once/month' to '6 times per day'.[18] At the health examination, the FFQ was checked and the participant's anthropometric measurements were assessed and recorded by one of the seven trained nurses according to a standard protocol.

Three years after the first health examination, all participants were invited for a second health check which included repeat measurements and a Follow-up Health Questionnaire. The latter recorded current information about bowel habits including bowel movement frequency ('How often on average do you have a bowel movement?'), consistency ('How would you describe the consistency?'), quantity ('When you have a bowel movement, about how much do you produce?'), feeling of discomfort during bowel movement ('Do you have any discomfort during your bowel movement?'), and laxative use ('Do you take laxatives?'). Bowel movement was categorised into seven subgroups (more than six times daily, four or five times daily, two or three times daily, daily, every four or five times a week, two or three times a week and less than once a week). Bowel movement consistency was assessed in three levels (hard, soft and loose). Similarly bowel movement quantity had three categories (small, medium and large). In addition, any discomfort during bowel movement was recorded (no, yes). The questionnaire also asked about whether participants used laxatives (no, yes), the frequency of laxative use (<1/d, daily, and >1/d) and brands of laxatives.

2.4. Statistical analysis

Simple associations were assessed with Pearson's χ^2 tests for two independent proportions. For the continuous variables, means were compared by t tests. Because of missing data, OR and 95% CI were calculated using unconditional logistic regression. Odds ratios were not substantially different when analyses were performed using conditional logistic regression.

Bowel movement frequency categories were combined into three levels (less than 4–5 stools per week, 7 stools per week and more than 2–3 stools per day). This study did not attempt to assess the association between frequency of laxative use and the development of CRC since statistical power might not be enough considering only 9% of cases and 11% of controls provided such information. Tests for trend were performed across categories of bowel habit and laxative use. Lifestyle factors could be either true confounders (independent risk factors) or determinants of bowel movement habits or laxative use, and therefore models with and without these factors were considered. For each bowel habit variable

(exposure) an age- and sex-adjusted model was constructed. A further lifestyle factor-adjusted model included body mass index (BMI) calculated in kilograms divided by height in meters squared and categorised as <25, 25 to <30 or ⩾30 kg/m^2; waist-to-hip ratio (WHR, continuous); current smoking status (never, former, current); intake of energy (kcal/d, continuous); alcohol (g/d, continuous); dietary fibre (g/d, continuous) and total meat (g/d, continuous). Adding weight, height, physical activity and use of HRT in the models did not materially alter the risk estimates and hence were not considered further.

Table 1 – Characteristics of colorectal cancer cases and controls in the EPIC-Norfolk study.

Characteristics[a]	Cases (n = 159)	Controls (n = 771)	P value[b]
Age (yr)	63.6 ± 8.0	64.2 ± 7.7	0.38
Sex			
Male	94 (59.1)	419 (54.4)	0.27
Female	65 (40.9)	352 (45.6)	
Bowel movement			
Frequency			
⩽4–5 stools/wk	15 (9.4)	103 (13.4)	0.03
7 stools/wk (daily)	88 (55.4)	472 (61.2)	
⩾2–3 stools/d	56 (35.2)	196 (25.4)	
Consistency[c]			
Hard	19 (11.9)	87 (11.3)	0.002
Soft	104 (65.4)	555 (72.0)	
Loose	18 (11.3)	33 (4.3)	
Quantity[c]			
Small	9 (5.7)	31 (4.0)	0.42
Medium	124 (78.0)	629 (81.6)	
Large	15 (9.4)	57 (7.4)	
Feeling[c]			
No discomfort	126 (79.2)	598 (77.6)	0.49
Discomfort	30 (18.9)	166 (21.5)	
Laxative use[c]			
No	138 (86.8)	652 (84.6)	0.75
Yes	16 (10.1)	83 (10.8)	
Frequency			
<1/d	9 (5.7)	53 (6.9)	0.74
Daily	5 (3.1)	23 (3.0)	
>1/d	1 (0.6)	11 (1.4)	
Weight (kg)	75.7 ± 13.5	74.1 ± 12.2	0.14
Height (cm)	168.5 ± 8.6	167.5 ± 9.1	0.20
WHR	0.9 ± 0.1	0.9 ± 0.1	0.14
BMI (kg/m^2)	26.6 ± 3.9	26.4 ± 3.4	0.44
Smoking status			
Never	68 (42.8)	355 (46.0)	0.47
Former	80 (50.3)	349 (45.3)	
Current	11 (6.9)	67 (8.7)	
Physical activity			
Low	93 (58.5)	468 (60.7)	0.60
High	66 (41.5)	303 (39.3)	
HRT use[c]			
Never	46 (28.9)	257 (33.3)	0.88
Former	9 (5.7)	41 (5.3)	
Current	10 (6.3)	54 (7.0)	
Energy intake (kcal/d)	2093 ± 639	2115 ± 628	0.69
Alcohol intake (g/d)	9 ± 12	9 ± 13	0.98
Dietary fibre intake (g/d)	18 ± 7	19 ± 6	0.13
Meat intake (g/d)			
Processed meat	24 ± 21	25 ± 21	0.88
Total meat and meat products	65 ± 40	71 ± 40	0.06

WHR = waist-to-hip ratio; BMI = body mass index; HRT use = hormone replacement therapy use.

a Mean (±SD) or number (%).

b P values relate to two-sided t-tests of equality of the means, or x^2 tests of association between cases and controls, as appropriate.

c Total number of subjects who reported stool consistency, quantity, feeling as well as use of laxatives and HRT may not add up to 930 due to missing information.

The final, mutually adjusted model included all bowel habit variables and use of laxatives in addition to the lifestyle factors.

In sensitivity analyses, we excluded cases recorded within three years of recruitment to address the possibility that preclinical CRC might influence bowel habits. All *P* values presented were two sided, and were considered statistically significant at the 5% level. All analyses were performed using STATA version 9.2 (Stata Corporation, College Station, Texas).

3. Results

During 12 years of follow-up, 159 cases with no history of CRC at baseline provided information on bowel habit and were therefore included in the analyses. Cases and controls were similar with respect to baseline characteristics such as weight, height, WHR, BMI and the distribution of smoking status, HRT use and physical activity (Table 1). Cases reported less energy, dietary fibre and total meat intake. However, none of these differences was statistically significant.

The proportion of cases having at least 2–3 stools per day was higher than that of controls, and the difference was statistically significant ($P = 0.03$). Eleven percent of cases reported loose stools, while only 4% of controls were in that category ($P = 0.002$). There was no difference in the distribution of the other bowel habit variables or laxative use between the two groups.

Associations between bowel habits or laxative use and CRC risk are presented in Table 2. In the age- and sex-adjusted model, having more than 2–3 stools per day was associated with a significantly increased risk of CRC (OR, 1.50; 95% CI, 1.03–2.18) when compared with having one stool per day. Further adjustment for several lifestyle factors did not alter the risk estimates. After adjusting for the other bowel habit variables, a similar though non-significant risk estimate was observed (OR, 1.39; 95% CI, 0.89–2.17). Less frequent bowel movement showed a decreased risk, but the association was not significant in any of the models (OR, 0.76; 95% CI, 0.36–1.58 in the fully adjusted model).

Having loose stools in comparison with soft stools was associated with an approximately 3-fold increased risk of CRC in all models. This was highly significant and the association still remained when both lifestyle factors and bowel habit variables were included in the model. The OR for the mutually adjusted model was 2.80 (95% CI, 1.41–5.56; *P* trend = 0.003). Similar results were seen for colon cancer. The association with loose stools was strengthened in colon cancer cases ($n = 114$) but the confidence intervals were wider (OR, 3.68; 95% CI, 1.85–7.32 and OR, 3.45; 95% CI, 1.62–7.34, for the lifestyle factors adjusted model and the fully adjusted model, respectively). Having loose stools in comparison with soft stools, however, was not associated with a rectal cancer risk in any of the models (data not shown).

Among participants who reported quantity of stools, those with small or large stools compared with medium were associated with a non-significant increased risk. Laxative use and feeling discomfort during bowel movement were not associated with CRC risk in any of the models.

The CRC cases with at least 2–3 stools per day compared with those with 7 stools per week reported having significantly more loose stools ($P < 0.001$) and more laxative use ($P = 0.001$), as well as less discomfort during bowel movement ($P = 0.02$). More cases with loose stools reported feeling discomfort ($P < 0.001$) while fewer reported laxative use than cases with soft stools ($P < 0.001$) (data not shown).

In a sensitivity analysis, after excluding CRC cases within three years of follow-up ($n = 30$), having loose stools was still a significant risk factor for CRC in all models (OR for the fully adjusted model, 2.31; 95% CI, 1.06-5.03).

4. Discussion

To our knowledge, this is the first prospective study using a nested case-control design that has reported a significant association between bowel movement consistency and CRC risk. In particular, having loose stools appeared to be a strong risk factor for incident CRC, especially for colon cancer, with an approximately 3-fold increased risk, and this was not substantially changed by adjusting for potential confounding factors or excluding the first three years of follow-up. Two recent Japanese cohort studies[8,13] did not find a significant association between self-reported diarrhoea and CRC risk, whilst a case-control study[11] observed that having loose stools significantly increased the risk for all subsites of CRC. Our study recorded actual bowel movement frequency and consistency instead of using the term 'diarrhoea' (which could have a different meaning for each individual without additional definition) and could therefore provide more detailed information about the exposure of interest in relation to CRC risk.

It has been suggested that diarrhoea or loose stools may have an irritant action on the mucosa of the large bowel, which could result in neoplasia.[9] It is possible that their effect may be mediated by prostaglandin E2 of which elevated levels are found in diarrhoea and which has been reported to enhance development of colon cancer in animal studies.[19–21] Even though diarrhoea is one of the common symptoms of CRC,[22,23] our finding of an increased CRC risk with loose stools persisted after excluding the first three years of follow-up. Few studies have attempted to explore high frequency of bowel movement as a possible risk factor for CRC. Findings from the Melbourne Colorectal Cancer Study[12] showed an almost 7-fold increased risk from having more than 3 stools per day compared with having between 3 stools per week and 3 per day. However, this risk estimate came from only 12 cases and two controls indicating limited statistical power. Additionally due to its retrospective case-control design, this study might not have been able to fully eliminate the possibility that reported bowel habits were symptoms of CRC.

By contrast, a recent large prospective study in Japan did not observe a significant association between CRC risk and frequent bowel movement (two or more per day) after adjusting for lifestyle factors, the hazard ratio (HR) in men and women was 1.03 and 1.16, respectively).[8] Our study did find a significantly increased risk for frequent bowel movement (at least two or three stools per day) when similar lifestyle factors were adjusted for, although the association was no longer

Table 2 – Adjusted odds ratios (95% CI) of colorectal cancer risk according to bowel movement habit and laxative use.

	Cases/controls	Age- and sex-adjusted model[a]		P value	Lifestyle factors adjusted model[b]		P value	Fully adjusted model[c]		P value
Bowel movement										
Frequency										
⩽4–5 stools/wk	15/103	0.79	(0.44–1.43)	0.49	0.78	(0.43–1.43)	0.42	0.76	(0.36–1.58)	0.46
7 stools/wk	88/472	1.00	(Ref)		1.00	(Ref)		1.00	(Ref)	
⩾2–3 stools/d	56/196	1.50	(1.03–2.18)	0.04	1.48	(1.01–2.17)	0.05	1.39	(0.89–2.17)	0.15
Consistency[d]										
Hard	19/87	1.21	(0.70–2.07)	0.50	1.27	(0.73–2.21)	0.40	1.42	(0.75–2.67)	0.28
Soft	104/555	1.00	(Ref)		1.00	(Ref)		1.00	(Ref)	
Loose	18/33	2.84	(1.54–5.25)	0.001	3.01	(1.60–5.66)	0.001	2.80	(1.41–5.56)	0.003
Quantity[d]										
Small	9/31	1.48	(0.69–3.18)	0.32	1.52	(0.70–3.33)	0.29	1.25	(0.50–3.15)	0.64
Medium	124/629	1.00	(Ref)		1.00	(Ref)		1.00	(Ref)	
Large	15/57	1.31	(0.72–2.39)	0.38	1.39	(0.75–2.56)	0.29	1.56	(0.80–3.03)	0.19
Feeling[d]										
No discomfort	126/598	1.00	(Ref)		1.00	(Ref)		1.00	(Ref)	
Discomfort	30/166	0.88	(0.57–1.37)	0.58	0.87	(0.56–1.35)	0.53	0.92	(0.54–1.57)	0.76
Laxative use[d,e]										
No	138/652	1.00	(Ref)	1.00		(Ref)		1.00	(Ref)	
Yes	16/83	0.97	(0.54–1.72)	0.90	0.96	(0.54–1.73)	0.90	0.92	(0.44–1.93)	0.83

95% CI = 95% confidence interval; BMI = body mass index; WHR = waist-to-hip ratio.

a Adjusted for age and sex.

b Additionally adjusted for BMI, WHR, smoking status, energy intake, alcohol intake, dietary fibre and total meat intake.

c Additionally adjusted for bowel movement and laxative use.

d Total number of subjects who reported stool consistency, quantity, feeling as well as laxative use may not add up to 930 due to missing information.

e Frequency of laxative use is not included in the final model due to missing values.

significant after further adjustment for other bowel habit variables.

A non-significant decreased risk estimate (OR, 0.78) was found between infrequent bowel movement and CRC risk in the current study. This is consistent with findings from two recent large prospective studies. The Nurses' Health Study which analysed 611 incident CRC cases after 12 years of follow-up demonstrated that having bowel movement every third day or less compared with once daily was not overall associated with CRC risk after adjustment for several lifestyle factors and use of laxatives.[7] Similarly, a recent large Japanese study with 479 incident CRC cases showed a non-significant multivariate HR of 0.97 in men and 0.75 in women with less than two or three bowel movements per week versus once per day.[8]

These findings appeared to be in conflict with the earlier hypothesis by Burkitt et al.[4,5] as well as results from previous case-control studies[12,14,24,25] and a meta-analysis[6] which showed that constipation or less frequent bowel movement associated with low fibre intake was a significant risk factor for CRC. However, these predominantly retrospective studies cannot exclude the effects of cancer itself, or recall and selection bias. Moreover, the majority of studies relied on self-reported information on constipation, which might not have been an appropriate indicator of delayed bowel transit time or actual bowel movement, as many people who complained of constipation in those studies also reported having stool frequencies and whole-gut transit times within the normal range.[26]

It is noteworthy that average fibre intake in this study was low and typical of the UK population,[18] and the level of fibre intake in the UK is relatively low compared to other European countries.[27,28] This association may differ in populations whose average fibre intake is high. Therefore, future studies in subjects with higher fibre intake are required to examine this hypothesis further.

When we compared laxative use to no laxative use there was no overall association with CRC. The risk estimates were not substantially changed when adjusted for lifestyle factors or the other bowel habit variables. These null findings are consistent with three recent studies; the Nurses' Health Study,[7] a population-based case-control study in North Carolina[14] and the Miyagi Cohort study.[15]

The current study has several strengths. Cases and controls came from the same population, avoiding any selection biases which are a major concern in case-control studies. Additionally, due to its prospective nature, data on bowel habits were collected prior to diagnosis of CRC, thus avoiding recall bias, and bias due to differential quality of information between cases and controls. The prospective design also made it possible to explore the temporal relationships between bowel habit and risk of CRC by excluding the cancer cases identified during the first three years of follow-up.

A concern was whether detection bias might have contributed to the observed association. This may be particularly true for loose stools where lower endoscopy is performed to rule out ulcerative colitis or Crohn's disease. In our study, 5 of 159 CRC cases were diagnosed with such diseases and only one person reported having loose stools. We therefore believe that such detection bias is unlikely to have played a role in our findings.

In this study we were able to control other dietary and lifestyle risk factors as well as bowel habits which have been hypothesised to confer an increased or decreased risk of CRC. Not many studies made mutual adjustment for bowel movement and laxative use in their models although it is possible that use of laxatives to treat infrequent bowel movement, rather than infrequent bowel movement itself, might possibly increase the risk of CRC.[29] Lastly, as the primary exposure of interest, actual bowel movement frequency and consistency were analysed rather than self-reported constipation or diarrhoea for which definitions could be ambiguous and equivocal for each subject. It is likely that participants might be more consistent when reporting bowel movement frequency than constipation or diarrhoea.

In spite of these strengths, other methodological limitations could have accounted for the findings. As the EPIC-Norfolk study was not specifically designed to detect the association between bowel habit and CRC risk, and relevant questions were only added during the follow-up period, not all participants provided bowel habit information, thus limiting the sample size for this analysis. Additionally, a significantly larger proportion of cases than controls was excluded from these analyses because of missing bowel frequency data, possibly causing underestimation of effect and reducing generalisability of the findings to the entire cohort. Similarly to previous epidemiologic studies, relying on self-reported data rather than measuring either actual bowel transit time or stool weight could be another limitation. Finally, although the prospective design of this study makes it less susceptible to reverse causality than retrospective case-control studies, and a sensitivity analysis also excluded cases recorded within three years of recruitment to further clarify any cause-effect relationship, it is still not certain whether bowel habit is a cause of CRC rather than a symptom, because the potential effect of residual confounding cannot be excluded completely, and the first three years of exclusion might not be long enough to eliminate this possibility.

In conclusion, there was no significant association between bowel movement frequency and CRC risk. However, self-reporting having loose stools was associated with an increased risk of CRC, even after multivariate adjustment or excluding the first three years of follow-up. Thus, the relationship between CRC and bowel habit merits further exploration, especially with regard to possible underlying mechanisms.

Conflict of interest statement

None declared.

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