

Constipation, laxative use and risk of colorectal cancer: The Miyagi Cohort Study

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Abstract

The objective of this study was to investigate the association between constipation or laxative use and the risk of colorectal cancer in Japanese men and women. In 1990, we delivered a self-administered questionnaire to 41 670 subjects who were 40–64 years old. During the seven years of follow-up, 251 incident cases of colorectal cancer were documented. Constipation was defined as a bowel movement frequency of less than daily. The multivariate relative risk (RR) of colorectal cancer for constipated subjects compared with those with daily bowel movements was 1.35 (95% Confidence Interval: 0.99–1.84). The RR for laxative users over non-users was 1.31 (0.88–1.95), and for frequent users (twice a week or more) it was 2.75 (1.48–5.09). When colorectal cancers were divided into colon cancers or rectal cancers, a significant association was found with colon cancer alone. Our results support the hypothesis that constipation or laxative use increases the risk of colon cancer.

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1. Introduction

The hypothesis that constipation or laxative use increases the risk of colorectal cancer has been controversial. Seven ecological studies of constipation have consistently found differences in faecal contents or bowel transit-time between high-risk and low-risk populations [1–7]. Twelve case-control studies have been conducted, and six of them found a positive association between constipation and the risk of colorectal cancer [8–19]. Moreover, a meta-analysis of nine case-control studies has shown a small, but significant, increase in risk associated with constipation [20]. By contrast, the results of the only prospective cohort study ever conducted did

not support an association between infrequent bowel movements and risk of colorectal cancer [21].

Eleven case-control studies of laxative use have been conducted, and five of them found a positive association between laxative use and risk of colorectal cancer [9,10,13–16,18,19,22–24]. Moreover, a meta-analysis of nine case-control studies showed a small, but significant, association [20]. By contrast, the findings in two prospective cohort studies have not supported an association between laxative use and the risk of colorectal cancer [21,25].

Most of the above studies had methodological limitations, including the use of a retrospective design [1–19,22–24] and failure to control sufficiently for potentially confounding variables, such as walking and food consumption [1–18,22–25]. Furthermore, few prospective studies have examined the association between constipation or laxative use and risk of colorectal cancer.

To further examine constipation or laxative use for an association with the risk of colorectal cancer, we

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conducted a population-based prospective cohort study in a rural area of Japan.

2. Patients and methods

2.1. Study cohort

We have reported the design of this prospective cohort study in detail elsewhere [26]. Briefly, between June and August 1990, we delivered a self-administered questionnaire to 51921 men and women who were 40–64 years old and living in 14 municipalities in Miyagi Prefecture in rural northern Japan. The questionnaires were delivered to, and collected at, subjects' residences by members of health promotion committees appointed by the municipal governments. The response rate to the questionnaire was 91.7% ($n=47605$).

The study protocol was approved by the institutional review board of the Tohoku University Graduate School of Medicine. We considered the return of a questionnaire signed by a subject to imply the subject's consent to participate in the study.

2.2. Assessment of constipation and laxative use

The questionnaire asked about demographic variables, education, personal and family history of cancer and other diseases, health habits, including frequency of bowel movements, frequency of laxative use, smoking, alcohol consumption, diet, physical activity, and self-reported height and weight.

To assess constipation, a multiple-choice question about the frequency of bowel movements during the previous year asked the subject to choose from four possible answers: once or more often per day (referred to as "daily"), once every 2–3 days, once every 4–5 days, and once every 6 days or less often. Because relatively few subjects chose "once every 4–5 days ($n=831$)" or "once every 6 days or less often ($n=122$)", we combined these two categories into one "once every 4 days or less often". We defined "constipation" as having fewer than "daily" bowel movements.

To assess laxative use, a multiple-choice question asked about whether subjects used laxatives during the previous year, and gave the subject three possible answers: never, occasionally, and twice a week or more often. The questionnaire did not ask about specific types or brands of laxatives. We defined "laxative user" as a subject who chose answers other than "never".

2.3. Follow-up

We used the population registries of the 14 municipalities to determine the vital and residential status of

the subjects from June 1, 1990 through December 31, 1997. We identified incident cancer cases by computerised record linkage with the Miyagi Prefectural Cancer Registry covering the study area [27].

Of the 47605 subjects who responded to the questionnaire, we excluded 914 subjects with a past history of cancer on the basis of self-report in the questionnaire or a record in the cancer registry. We also excluded 1840 subjects who did not respond to the question on bowel movement frequency as well as 3181 subjects who did not respond to the question on laxative use. Consequently, 41670 subjects (20044 men and 21626 women) remained for the purpose of this analysis. During the seven years of follow-up, 251 incident cases of colorectal cancer were identified, of which 156 were colon cancer (103 men and 53 women) and 95 were rectal cancer (57 men and 38 women).

2.4. Statistical analysis

We counted person-years of follow-up for each subject from June 1, 1990 until the date of diagnosis of colorectal cancer, date of emigration outside the study district (because of logistical limitations), date of death, or the end of the study period (December 31, 1997), whichever occurred first. A total of 306091 person-years accrued.

We used the Cox proportional-hazards regression to estimate the relative risk (RR) and 95% Confidence Interval (CI) of colorectal cancer according to the frequency of bowel movements and laxative use and to adjust for potentially confounding variables by using the PHREG procedure of the SAS version 8.2 statistical software package (Cary, NC, USA). In addition to gender and age, we considered the following variables as potential confounders: cigarettes smoking (never smoked, smoked in the past, currently smoking 1–19 cigarette per day, or currently smoking 20 or more cigarettes per day), alcohol consumption (never drank alcohol, drank in the past, currently drinking 22.7 g or less alcohol per day, or currently drinking 22.8 g or more alcohol per day), body mass index (BMI) in kg/m² (18.4 or lower, 18.5–24.9, 25.0 or higher), education (upto 15 years of age, from 16 to 18 years of age, or to 19 years or older), family history of colorectal cancer (presence or absence), consumption frequency of pork, green vegetables and orange (almost every day, 3–4 times per week, 1–2 times per week, 1–2 times per month, or rarely), daily walking time as a measure of non-occupational physical activity (60 min or more, 30–60 min, 30 min or less).

The "daily" category was used as the reference category to calculate the RRs associated with the frequency of bowel movements. "Every 2–3 days" and "every 4 days or less" were treated as separate categories, as well as the combined category "less than daily". To calculate

the RRs associated with laxative use, the “never” category was used as the reference category and referred to as “non-users”. “Occasionally” and “twice a week or more often” were treated as the combined category “laxative user” in addition to the separate categories designated “less than twice a week” and “twice or more often a week”, respectively.

To minimise any confusion between bowel habit change as a symptom of colorectal cancer and as a risk factor, we repeated all analyses after excluding colorectal cancer cases diagnosed in the first 3 years of follow-up ($n=71$). All P values were two-tailed.

3. Results

Table 1 shows the number of men and women cross-classified by frequency of bowel movements and laxative use. Prevalence of constipation (defined as less than daily bowel movements) was higher among the women (31.8%) than among the men (11.9%). Prevalence of laxative use was also higher among the women (16.3%) than among the men (4.8%). Constipated men were more likely to use laxatives than men without constipation (14.2% and 3.5%, respectively), and constipated women were more likely to use laxatives than women without constipation (32.0% and 9.0%, respectively). Nevertheless, substantial proportions of both constipated men and women (85.8% and 68.0%, respectively) did not report the use of laxatives.

Table 2 shows several key characteristics of the men and women according to the frequency of bowel move-

ments and laxative use. Among the men, the constipated subjects were less likely to be obese, consume alcohol or walk. Laxative users were older, less likely to consume alcohol, walk or consume pork every day. Among the women, the constipated subjects were less likely to be obese, walk or consume vegetables every day. Laxative users were more likely to smoke and consume alcohol, but less likely to walk or consume pork every day.

Table 3 shows the RRs of colorectal cancer according to bowel movement frequency. We observed a modest increase in risk among subjects with constipation (less than daily bowel movements) compared with subjects without constipation (daily bowel movements), with the gender- and age-adjusted RR (95% CI) of 1.32 (0.97–1.80). We did not find a linear increase in risk associated with a lower frequency of bowel movement (trend $P=0.16$), partly because of the small number of subjects with a very low bowel frequency (every 4 days or less). These results remained basically unchanged after multivariate adjustment of potential confounders and after the exclusion of colorectal cancer cases identified during the first three years of follow-up.

Table 3 also shows the RRs of colorectal cancer according to laxative use. We observed a modest increase in risk among laxative users compared with non-users, with the gender- and age-adjusted RR (95% CI) of 1.31 (0.88–1.95). We found a linear increase in risk associated with a higher frequency of laxative use (trend $P=0.02$), with the gender- and age-adjusted RR (95% CI) of 2.76 (1.50–5.07) for subjects who used laxatives twice a week or more often. These results remained qualitatively similar after multivariate adjustment for potential confounders and after the exclusion of colorectal cancer cases diagnosed in the first three years of follow-up.

When the data for men and women were analysed separately, the multivariate RR (95% CI) for subjects with constipation compared with subjects without constipation was 1.24 (0.78–1.97) for men and 1.45 (0.94–2.22) for women. The multivariate RR (95% CI) for laxative users compared with non-users were 1.55 (0.87–2.76) for men and 1.18 (0.68–2.03) for women.

Table 4 shows the multivariate RRs for colon cancer and rectal cancer separately. We observed a higher risk associated with constipation and laxative use only for colon cancer and not for rectal cancer.

We conducted further analyses in which the presence or absence of constipation and laxative use were entered into the multivariate model simultaneously. The results were not altered materially, with multivariate RR (95% CI) of 1.32 (0.96–1.82) for constipation and 1.21 (0.80–1.82) for laxative use. We also divided subjects into four groups according to whether they were positive for constipation or laxative use, both, or neither. Compared with the subjects who were not constipated and did not use laxatives (30455 subjects including 186

Table 1
Number of the subjects divided by bowel movement and use of laxatives

	Bowel movement frequency		
	Daily or more	Every 2–3 days	Every 4 days or less
<i>Men and women</i>			
Laxative use			
Non-user	30455	6290	437
<2 times/week	1555	1725	389
≥2 times/week	391	301	127
<i>Men</i>			
Laxative use			
Non-user	17038	1944	101
<2 times/week	524	237	44
≥2 times/week	99	46	11
<i>Women</i>			
Laxative use			
Non-user	13417	4346	336
<2 times/week	1031	1488	345
≥2 times/week	292	255	116

Table 2
Characteristics of the subjects according to bowel movement and use of laxative

Bowel movement	Men			Women		
	Daily or more	Every 2–3 days	Every 4 days or less	Daily or more	Every 2–3 days	Every 4 days or less
No. of subjects	17661	2227	156	14740	6089	797
Age (years), means \pm SD	51.8 \pm 7.6	51.0 \pm 7.7	53.5 \pm 7.7	52.8 \pm 7.3	51.1 \pm 7.5	50.1 \pm 7.4
BMI in kg/m ² \geq 25.0 (%)	27.9	23.6	23.3	33.5	26.8	22.4
Current smoker (%)	61.2	62.9	61.5	8.5	9.6	16.9
Current drinker (%)	78.0	70.8	59.4	25.0	27.4	28.4
Education \geq 19 year (%)	14.2	14.1	12.2	12.7	13.5	10.0
Family history of colorectal cancer (%)	1.5	1.3	1.7	1.5	1.7	1.5
Walking time >60 min/day (%)	460	410	29.7	47.8	41.2	38.8
Pork intake almost every day (%)	2.8	2.7	6.3	3.0	2.8	3.5
Vegetables intake almost every day (%)	20.8	16.3	19.5	28.6	22.6	21.2
Orange intake almost every day (%)	18.0	16.0	15.4	37.3	34.8	34.3
Use of laxative	Non-user	<2 times/week	\geq 2 times/week	Non-user	<2 times/week	\geq 2 times/week
No. of subjects	19083	805	156	18099	2864	663
Age (years), means \pm SD	51.5 \pm 7.6	53.5 \pm 7.6	54.5 \pm 7.6	52.1 \pm 7.4	51.6 \pm 7.4	51.9 \pm 7.2
BMI in kg/m ² \geq 25.0 (%)	27.6	25.0	31.1	30.8	33.3	29.4
Current smoker (%)	61.6	58.5	50.0	8.0	13.1	16.3
Current drinker (%)	77.7	67.1	50.9	24.9	29.2	32.8
Education \geq 19 year (%)	14.5	15.3	15.8	12.8	11.9	19.6
Family history of colorectal cancer (%)	1.4	1.4	3.0	1.5	1.8	2.6
Walking time >60 min/day (%)	45.3	38.4	31.1	46.8	39.0	33.6
Pork intake almost every day (%)	6.1	2.4	0.7	3.0	2.3	3.3
Vegetables intake almost every day (%)	20.2	20.9	24.2	27.2	23.5	22.3
Orange intake almost every day (%)	17.7	18.7	24.0	36.9	34.9	34.1

SD, standard deviation; BMI, body mass index.

Table 3
Relative risk of colorectal cancer according to bowel movements and use of laxative

Bowel movement	Daily or more	Less than daily			P for trend
		Total	Every 2–3 days	Every 4 days or less	
No. of cases of colorectal cancer	196	55	52	3	
Person-years of follow-up	238 106	67985	61064	6921	
Gender- and age-adjusted RR	1.00	1.32 (0.97–1.80)	1.38 (1.01–1.89)	0.77 (0.25–2.43)	0.16
P-value (versus daily or more)		0.07			
Multivariate RR 1	1.00	1.35 (0.99–1.84)	1.40 (1.02–1.93)	0.80 (0.25–2.51)	0.13
P-value (versus daily or more)		0.06			
Multivariate RR 2	1.00	1.30 (0.89–1.88)	1.38 (0.95–2.01)	0.38 (0.05–2.70)	0.38
P-value (versus daily or more)		0.17			
Use of laxative	Non-user	Laxative user			P for trend
		Total	<2 times/week	>2 times/week	
No. of cases of colorectal cancer	222	29	18	11	
Person-years of follow-up	273 400	32691	26785	5906	
Gender- and age-adjusted RR	1.00	1.31 (0.88–1.95)	0.99 (0.61–1.62)	2.76 (1.50–5.07)	0.02
P-value (versus non-user)		0.18			
Multivariate RR 1	1.00	1.31 (0.88–1.95)	1.00 (0.61–1.63)	2.75 (1.48–5.09)	0.02
P-value (versus non-user)		0.18			
Multivariate RR 2	1.00	1.10 (0.67–1.80)	0.82 (0.44–1.52)	2.40 (1.11–5.18)	0.26
P-value (versus non-user)		0.72			

The multivariate relative risk (RR) has been adjusted for gender; age (in years); cigarettes smoking (never smoked, smoked in the past, currently smoking 1–19 cigarettes per day, or currently smoking 20 or more cigarettes per day); alcohol consumption (never drank alcohol, drank in the past, currently drinking 22.7 g or less alcohol per day, or currently drinking 22.8 g or more alcohol per day); body mass index in kg/m² (18.4 or lower, 18.5–24.9, or 25.0 or higher); education (upto 15 years of age, from 16 to 18 years, or 19 years or older); family history of colorectal cancer (presence or absence); pork intake (almost every day, 3–4 times/week, 1–2 times/week, 1–2 times/month, few); green vegetables intake (same as pork); orange intake (same as pork); walking time per day (60 min or more, 30–60 min, 30 min or less). RR2 denotes the RR excluding the case that were diagnosed in the first three years of follow-up. Values in parentheses are 95% CI.

Table 4

Relative risk of colon cancer or rectal cancer alone according to bowel movements and use of laxative

Bowel movement	Colon cancer			Rectal cancer	
	Daily or more	Less than daily		Daily or more	Less than daily
No. of cases of colon cancer	120	36	No. of cases of rectal cancer	76	19
Gender- and age-adjusted RR	1.00	1.48 (1.01–2.18)	Gender- and age-adjusted RR	1.00	1.10 (0.65–1.84)
<i>P</i> -value (<i>versus</i> daily or more)		0.05	<i>P</i> -value (<i>versus</i> daily or more)		0.73
Multivariate RR	1.00	1.47 (1.00–2.17)	Multivariate RR	1.00	1.16 (0.69–1.95)
<i>P</i> -value (<i>versus</i> daily or more)		0.05	<i>P</i> -value (<i>versus</i> daily or more)		0.59
Laxative use	Laxative user			Laxative user	
	Non-user	Laxative user		Non-user	Laxative user
No. of cases of colon cancer	136	20	No. of cases of rectal cancer	86	9
Gender- and age-adjusted RR	1.00	1.52 (0.94–2.45)	Gender- and age-adjusted RR	1.00	1.00 (0.50–2.01)
<i>P</i> -value (<i>versus</i> non-user)		0.09	<i>P</i> -value (<i>versus</i> non-user)		1.00
Multivariate RR	1.00	1.48 (0.91–2.40)	Multivariate RR	1.00	1.04 (0.52–2.10)
<i>P</i> -value (<i>versus</i> non-user)		0.11	<i>P</i> -value (<i>versus</i> non-user)		0.91

The multivariate relative risk (RR) has been adjusted for gender; age (in years); laxative use frequency (never, less than 2 times/week, 2 times/week or more); cigarettes smoking (never smoked, smoked in the past, currently smoking 1–19 cigarettes per day, or currently smoking 20 or more cigarettes per day); alcohol consumption (never drank alcohol, drank in the past, currently drinking 22.7 g or less alcohol per day, or currently drinking 22.8 g or more alcohol per day); body mass index in kg/m² (18.4 or lower, 18.5–24.9, or 25.0 or higher); education (upto 15 years of age, from 16 to 18 years, or 19 years or older); family history of colorectal cancer (presence or absence); pork intake (almost every day, 3–4 times/week, 1–2 times/week, 1–2 times/month, few); green vegetables intake (same as pork); orange intake (same as pork); walking time per day (60 min or more, 30–60 min, 30 min or less). Values in parentheses are 95% CI.

colorectal cancer cases), the multivariate RRs (95% CI) for the subjects with constipation and non-users of laxatives (6727 including 36 cases), the subjects without constipation and users of laxatives (1946 including 10 cases), and the subjects who were constipated in spite of the use of laxatives (2542 including 19 cases) were 1.18 (0.82–1.70), 0.91 (0.48–1.73) and 1.85 (1.13–3.02), respectively.

4. Discussion

The hypothesis that constipation increases the risk of colorectal cancer is based on evidence suggesting several possible mechanisms. First, bile acids [28,29], fecapentaene-12 [30] and ammonium acetate [31], present in faeces are reported to have cancer-promoting effects. Second, constipation causes bowel epithelial cells to come into contact with faeces for longer, and the significance of this contact with faeces has been demonstrated in several animal studies [32–34]. As the rectum is thought to be empty during constipation [35], this hypothesis may be more valid for colon cancer than for rectal cancer.

In this study, we found a modest, marginally significant, association between constipation and an increased risk of colon cancer. This is the first prospective cohort study on constipation and the risk of colorectal cancer to include both men and women. The Nurses' Health Study in the United States is the only other previous prospective study of bowel movement frequency and colorectal cancer [21]. That study followed 84 577 female nurses for 12 years and found no increase in the risk of

colorectal cancer, with a multivariate RR (95% CI) of 0.94 (0.69–1.28) for constipated women (having a bowel movement every 3 days or less often) compared with women with daily bowel movements. However, the results of the Nurses' Health Study did not necessarily exclude the possibility of a modest increase in risk, as suggested by the 95% CI of the RR.

Some ingredients of 'over-the-counter' laxatives have been reported to have cancer-promoting or -initiating activity in *in vitro* and *in vivo* experiments [36–39]. The results of our study are consistent with the findings of these laboratory experiments in showing an increased risk of colon cancer associated with laxative use. Two prospective studies have examined the association between laxative use and the risk of colorectal cancer. The first study [25] followed 11 888 Caucasian Americans for four and a half years and documented 126 cases of colorectal cancer. The RR (95% CI) for men and women who used laxatives daily compared with non-users was 1.32 (0.6–2.7) and 1.38 (0.7–2.6), respectively. The second study, the Nurses' Health Study [21], did not find any association and the multivariate RR (95% CI) was 1.00 (0.72–1.40) for women who used laxatives weekly to daily compared with non-users. The subjects of that study were all women, and our results are consistent with its findings that laxative use is not positively associated with an increased risk of colorectal cancer in women.

When assessing the associations between constipation, laxative use and risk of colorectal cancer, the temporal relationships among them must be taken into account in order to determine whether constipation is a symptom of the colorectal cancer or a cause of the

colorectal cancer. Case-control studies are particularly susceptible to this bias, because bowel movements and laxative use in the past were asked after case subjects had been diagnosed with colorectal cancer. We were able to minimise such bias by using a prospective study design, and by excluding the cancer cases identified during the first three years of follow-up.

Our study has two limitations. First, because the number of colorectal cancer cases was small, the increase in risk associated with constipation or laxative use was only of marginal statistical significance. Second, we did not specifically ask about the types or brands of laxatives used, although most laxatives exhibiting carcinogenic properties are irritant laxatives rather than bulk laxatives, lubricant laxatives or saline purgatives.

In conclusion, the findings in this population-based, prospective cohort study in middle-aged Japanese men and women support the hypothesis that constipation and laxative use increase the risk of colon cancer.

Conflict of interest

None.

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