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# Association of Habitual Preoperative Dietary Fiber Intake With Complications After Colorectal Cancer Surgery

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**IMPORTANCE** Postoperative complications are associated with increased morbidity and mortality among patients with colorectal cancer. As a modifiable factor associated with gut health, dietary fiber intake is of interest with regard to the risk of complications after surgery for colorectal cancer.

**OBJECTIVE** To examine the association between preoperative dietary fiber intake and risk of complications after surgery for colorectal cancer.

**DESIGN, SETTING, AND PARTICIPANTS** This cohort study used data from the Colorectal Longitudinal, Observational Study on Nutritional and Lifestyle Factors (COLON) study, which recruited adult patients with colorectal cancer at any stage at diagnosis from 11 hospitals in the Netherlands between August 2010 and December 2017. The present study included patients with stage I to IV colorectal cancer who underwent elective abdominal surgery. Data were analyzed between December 2019 and September 2020.

**EXPOSURES** Habitual dietary fiber intake was assessed at diagnosis using a 204-item food frequency questionnaire.

**MAIN OUTCOMES AND MEASURES** Any complications, surgical complications, and anastomotic leakage occurring during the 30 days after surgery for colorectal cancer. The association between fiber intake and risk of postoperative complications was assessed using logistic regression analyses. Additional analyses stratified by sex, tumor location, and fiber source were performed.

**RESULTS** Among the 1399 patients included in the analysis, the median age at inclusion was 66 years (interquartile range, 61-72 years) and 896 (64%) were men. Any complications occurred in 397 patients (28%), and surgical complications occurred in 235 patients (17%). Of 1237 patients with an anastomosis, 67 (5%) experienced anastomotic leakage. Higher dietary fiber intake (per 10 g per day) was associated with a lower risk of any complications (odds ratio [OR], 0.75; 95% CI, 0.62-0.92) and surgical complications (OR, 0.76; 95% CI, 0.60-0.97), whereas no association with anastomotic leakage was found (OR, 0.97; 95% CI, 0.66-1.43). Among women, higher dietary intake was associated with any complications (OR, 0.64; 95% CI, 0.44-0.94), whereas there was no association among men (OR, 0.79; 95% CI, 0.63-1.01). Fiber intake from vegetables (per 1 g per day) was inversely associated with any (OR, 0.90; 95% CI, 0.83-0.99) and surgical (OR, 0.87; 95% CI, 0.78-0.97) complications.

**CONCLUSIONS AND RELEVANCE** In this cohort study, higher habitual dietary fiber intake before surgery was associated with a lower risk of postoperative complications among patients with colorectal cancer. The findings suggest that improving preoperative dietary fiber intake may be considered in future prehabilitation programs for patients undergoing surgery for colorectal cancer.

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Supplemental content

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Surgery is the indicated treatment modality for most patients with colorectal cancer (CRC) in Western countries.[1] After tumor resection, severe complications, such as anastomotic leakage, infections, or ileus, occur in 15% to 50% of patients.[2-5] These postoperative complications affect quality of life, length of hospital stay, and readmission and mortality rates.[5-9] Moreover, complicated recovery after surgery for CRC is associated with increased resource utilization and hospital costs.[10]

Some demographic and clinical characteristics, such as current smoking, male sex, obesity, and comorbidities, have been associated with postoperative complications in patients with CRC.[2,5,11-15] Emerging evidence suggests that impaired gut health may also be associated with risk of postoperative complications.[16,17] As a modifiable factor linked to gut health,[18,19] dietary fiber intake is of specific interest with regard to the risk of complications after gastrointestinal surgery.

Dietary fiber represents oligosaccharides and polysaccharides that resist degradation by human enzymes in the gastrointestinal tract.[20] Bacterial fermentation of dietary fiber occurs predominantly in the colon and results in production of metabolites, such as short-chain fatty acids (SCFAs), that become available to the host.[21] In addition to these metabolites, fecal bulking, effect on transit time, and other yet to be confirmed mechanisms have been linked to the positive health effects of dietary fiber.[18,21] Earlier work in model species showed that inadequate fiber intake resulted in an impaired mucosal barrier and enhanced pathogen susceptibility.[22,23] Both these phenomena are deemed relevant to the pathogenesis of postoperative complications in patients with CRC.[16,24]

To date, dietary fiber intake has not been extensively considered in multimodal prehabilitation programs, such as the Enhanced Recovery After Surgery guidelines, which mainly focus on prevention of malnutrition through protein and energy intake and specific vitamins and minerals.[25,26] Therefore, the aim of this study was to examine the association between habitual dietary fiber intake before surgery and the risk of postoperative complications in patients with stage I-IV CRC, with consideration of potential confounding factors.

### Key Points

**Question** Is habitual preoperative dietary fiber intake associated with risk of complications after surgery for colorectal cancer?

**Findings** In this cohort study of 1399 patients with colorectal cancer who underwent surgery, higher habitual dietary fiber intake before surgery was associated with a lower risk of any postoperative complications and surgical postoperative complications. Among patients with an anastomosis, dietary fiber intake was not associated with risk of anastomotic leakage.

**Meaning** The findings suggest that improving preoperative dietary fiber intake may be considered as a strategy in future prehabilitation programs for patients undergoing surgery for colorectal cancer.

## Methods

### Patients

This cohort study used data from the Colorectal Longitudinal, Observational Study on Nutritional and Lifestyle Factors (COLON) study.[27] The COLON study is a prospective cohort study initiated to examine associations of diet and other lifestyle factors with clinical outcomes in patients with CRC. In brief, adult patients (age ≥18 years) with cancer at any stage were recruited directly after diagnosis and before surgery from 11 hospitals in the Netherlands. Patients were not included if they did not speak Dutch, had a history of CRC or bowel resection, or had a diagnosis of inflammatory bowel disease, hereditary CRC, or a mental health condition preventing completion of the study questionnaires. All patients provided written informed consent. The COLON study was reviewed and approved by the Committee on Research Involving Human Subjects, Arnhem-Nijmegen, the Netherlands. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

We included 1641 patients recruited between August 2010 and December 2017 and for whom linkage with the clinical databases was completed at the time of analysis (**Figure 1**). Patients with stage 0 disease (n = 3) and those who did not undergo surgery (n = 12) were excluded. Patients who underwent nonelective (n = 15) or transanal (n = 13) surgery or received hyperthermic intraperitoneal chemotherapy (n = 4) and those with missing data on fiber intake (n = 125) were excluded. In addition, patients with missing outcome data (n = 70 for any complications, n = 12 for surgical complications, and n = 13 for anastomotic leakage) were excluded, resulting in a study population of 1399 patients.

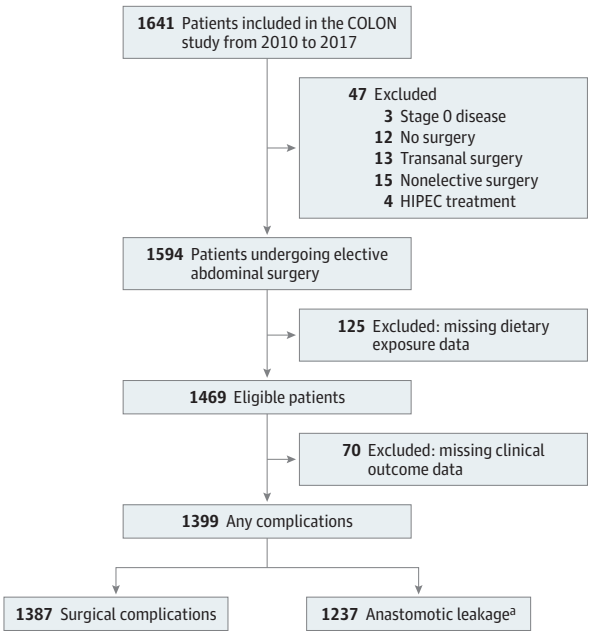
### Dietary Fiber Intake

Data on habitual dietary intake during the 1 month before diagnosis were collected via a self-administered and semiquantitative 204-item food frequency questionnaire (FFQ) completed shortly after diagnosis.[28,29] Total dietary fiber intake was calculated based on the frequency of intake, number of portions, and standard portion sizes of relevant items using data from the 2011 Dutch food composition tables.[30] To further explore different fiber sources, intake of fiber from fruits, vegetables, cereals, whole grains, and refined grains was analyzed separately because these were the major fiber sources in this population.

### Clinical Outcomes

Disease characteristics and clinical outcome data were obtained from the Dutch Colorectal Audit,[31] which reports the occurrence of postoperative complications within 30 days after surgery. Clinical outcomes considered for this study were any or surgical postoperative complications and anastomotic leakage. Any complications included surgical postoperative complications and other (eg, pulmonary, neurological, or cardiovascular) postoperative complications. Surgical complications included surgical site infection, anastomotic leakage, or postoperative ileus, among others. Anastomotic leakage was only

Figure 1. Flow Diagram of Patients With Colorectal Cancer Who Underwent Elective Abdominal Tumor Resection




COLON indicates Colorectal Longitudinal, Observational Study on Nutritional and Lifestyle Factors study; HIPEC, hyperthermic intraperitoneal chemotherapy.

[a] Of 1250 patients with anastomosis.

considered in patients with an anastomosis (n = 1250). Anastomotic leakage was defined as an anastomotic leak that required a reintervention within 30 days after the surgical procedure. Tumor stage, physical status classification of the American Association of Anesthesiologists (ASA), surgical procedures, and other treatment characteristics were also obtained from the Dutch Colorectal Audit.

## Descriptive Data and Covariates

Additional information on general and lifestyle factors was obtained through questionnaires completed at the time of diagnosis. Body mass index was calculated based on self-reported weight and height. Smoking status was defined as current, former, or never. The validated Short Questionnaire to Assess Health-enhancing Physical Activity (SQUASH) was used to assess time spent doing moderate to vigorous physical activity, as described elsewhere.[32,33]

## Statistical Analysis

Data were analyzed between December 2019 and September 2020. Patients' characteristics are presented as descriptive data using medians and interquartile ranges (IQRs) or numbers and percentages. The association between fiber intake and risk of postoperative complications was assessed using logistic regression analyses. Total dietary fiber intake was considered continuously (per 10 g per day) and in tertiles, with the lowest tertile (T1) being the reference category. For dietary fiber intake from individual fiber sources, intake was considered per 1 g per day because intake from these sources is lower than total dietary fiber intake. *P* values for trends were calculated by including median fiber intake for each tertile as an independent continuous variable in the model, with $P < .05$ indicating statistical significance. Crude analyses were adjusted for age and sex. To consider potential confounding, analyses were further adjusted for smoking status (former, current, or never), ASA classification (I, II, or III-IV), and tumor location (colon, rectum) because these variables are known to be associated with postoperative complications in patients with CRC[13,34,35] or with dietary fiber intake[36,37] or were used as covariates in previous studies.[38,39] Other potential confounders, such as body mass index, tumor stage (I, II, III, or IV), physical activity (minutes per week), and energy intake (kcal per day) were added one by one to the models. When one of these variables changed the effect estimate by more than 10%, the variable was included in the model as a covariate.

Stratified analyses were performed for sex because previous studies[40,41] suggested that effects of fiber on microbiota composition, SCFA production, and immune parameters, at least in rodent models, may be sex specific. Stratified analyses for tumor location (colon vs rectum) were performed because it was hypothesized that associations between fiber intake and postoperative complications may differ owing to pronounced differences in microbiota composition and molecular tumor features in these locations.[42,43] In stratified analyses, results are presented per 10-g/d increase in dietary fiber intake and not per tertile of dietary fiber intake because the number of patients per group would be insufficiently small. *P* values for interaction were calculated by adding product terms for dietary fiber intake × sex or dietary fiber intake × tumor location to the main models, with adjustment for the aforementioned confounders.

Sensitivity analyses were performed excluding patients with stage IV cancer or an unknown stage of cancer (n = 87) because the risk of complications might be predominantly associated with compromised health rather than dietary aspects among these patients. We primarily focused on absolute fiber intake because the actual amount of fiber passing through the gastrointestinal tract might be most important from a biological point of view. To study intake of fiber relative to energy intake, sensitivity analyses were performed using energy-adjusted fiber intake as the exposure variable. The residual method was used to calculate energy-adjusted fiber intake,[44] and energy intake (in kcal per day) was added to the previously mentioned covariates in the models. We also excluded patients who completed the FFQ more than 30 days before or less than 14 days after surgery for CRC or with a missing FFQ completion date (n = 280). Finally, to explore whether a stoma or neoadjuvant treatment (chemotherapy and/or radiotherapy) affected the associations, sensitivity analyses excluding patients with a stoma created during surgery (n = 419) or who received neoadjuvant treatment (n = 335) were performed. Stratified and sensitivity analyses were performed for any postoperative complications as the outcome because the number of patients in the subgroups would be insufficiently small for the other outcomes. All analyses were performed using SPSS, version 25 (IBM Corp). A 2-sided $P < .05$ was considered statistically significant.

## Results

In total, 1399 patients were included in this study (Figure 1). The median time between completion of the FFQ and surgery was 8 days (IQR, 2-17 days). The median age of the patients was 66 years (IQR, 61-72 years), 896 (64%) were men, and most had a diagnosis of colon cancer (956 [68%]) vs rectal cancer (443 [32%]) (**Table 1**). Median habitual fiber intake was 19.6 g/d (IQR, 15.8-24.2 g/d), and 125 patients (9%) adhered to the national recommendation for dietary fiber intake (≥3.4 g/MJ).[45] Any postoperative complications were registered for 397 patients (28%), with surgical complications occurring in 235 patients (17%) and anastomotic leaks in 67 of 1237 patients with an anastomosis (5%).

Compared with the patients who did not have complications within 30 days after the surgical procedure (n = 1002), patients who experienced any complications (n = 397) more often were men (279 [70%] vs 617 [62%]), reported current smoking (63 [16%] vs 88 [9%]), had a diagnosis of rectal cancer (172 [43%] vs 271 [27%]), had received neoadjuvant treatment (134 [34%] vs 201 [20%]), and had an ASA classification of III or IV (75 [19%] vs 89 [9%]). Patients with complications also more often received a stoma during surgery (170 [44%] vs 229 [23%]), were more often admitted to the intensive care unit (88 [23%] vs 17 [2%]), and had a longer hospital length of stay (median, 11 days [IQR, 7-18 days] vs 5 days [IQR, 4-7 days]) (Table 1).

Compared with patients with the lowest fiber intake (T1) (n = 466), patients with the highest fiber intake (T3) (n = 466) were more often men (326 [70%] vs 272 [58%]), less often reported current smoking (40 [9%] vs 66 [14%]), had higher energy intake (median, 2222 kcal/d [IQR, 1966-2580 kcal/d] vs 1439 kcal/d [IQR, 1235-1655 kcal/d]), and were more physically active (median, 870 minutes/week [IQR, 480-1418 minutes/week] vs 450 minutes/week [IQR, 240-888 minutes/week]). Patients with the highest fiber intake also had lower rates of any postoperative complications (117 [25%] vs 151 [32%]) (eTable in the Supplement).

In adjusted logistic regression analyses, higher dietary fiber intake (per 10 g/d) was significantly associated with a lower risk of any complications (odds ratio [OR], 0.75; 95% CI, 0.62-0.92) and surgical complications (OR, 0.76; 95% CI, 0.60-0.97). For patients with an anastomosis, intake of fiber was not associated with occurrence of anastomotic leakage (OR, 0.97; 95% CI, 0.66-1.43) (**Table 2**).

In stratified analyses, higher dietary fiber intake was associated with a lower risk of any postoperative complications in women (OR, 0.64; 95% CI, 0.44-0.94), whereas there was no association for men (OR, 0.79; 95% CI, 0.63-1.01) ($P$ = .28 for interaction), although the risk estimates pointed in the same direction and the difference between men and women was relatively small. In stratified analyses for tumor location, dietary fiber intake was not associated with risk of any complications in patients with colon cancer (OR, 0.78; 95% CI, 0.61-1.01), but there was an association between dietary fiber intake and risk of any complications in patients with rectal cancer (OR, 0.71; 95% CI, 0.51-0.98) ($P$ = .89 for interaction) (**Table 3**).

In sensitivity analyses, exclusion of patients with stage IV or unknown cancer stage (n = 87), patients with a stoma or with unknown stoma status (n = 419), patients who completed the FFQ more than 30 days before or less than 14 days after surgery or with unknown completion date (n = 280), and patients who received neoadjuvant treatment (n = 335) did not substantially change results compared with the main analyses. Considering energy-adjusted fiber intake in sensitivity analyses did not substantially change effect estimates compared with the main analyses, although there were no longer significant associations between higher fiber intake and any (OR, 0.76; 95% CI, 0.57-1.02) and surgical (OR, 0.73; 95% CI, 0.51-1.03) postoperative complications.

To further explore the potential relevance of the different sources of fiber, we also conducted the main analyses with intake of dietary fiber (now per 1-g/d increase) specified for the main sources of dietary fiber in this population (fiber from cereals, refined grains, whole grains, fruits, and vegetables). Among the fiber sources, the associations with intake of fiber from vegetables were strongest; for any complications, the OR was 0.90 (95% CI, 0.83-0.99) and for surgical complications, the OR was 0.87 (95% CI, 0.78-0.97) (**Figure 2**).

## Discussion

To our knowledge, this is the first study showing that higher habitual dietary fiber intake before surgery was associated with a lower risk of any or surgical postoperative complications in patients with CRC. Dietary fiber intake was not associated with risk of anastomotic leakage among patients with anastomosis. Higher dietary fiber intake was associated with a lower risk of any postoperative complications among women but not among men, although the difference in risk estimates between men and women was relatively small. Fiber from vegetables was inversely associated with any complications or surgical complications.

The literature on the association between habitual and preoperative dietary fiber intake and postoperative outcomes is scarce. Berstad et al[46] compared patients with CRC with (n = 29) and without (n = 71) postoperative complications and did not observe a difference in daily fiber intake (2.7 g/MJ vs 2.8 g/MJ) or the proportion of patients who adhered to the recommendation for fiber intake (≥3g/MJ) (35% vs 31%). However, that study was based on a relatively small population, and analyses were not adjusted for relevant confounding factors. Moreover, adherence to recommendations for fiber intake was high compared with that in the population in the present study. Similar to the US and several other European countries,[20,47,48] fiber intake is relatively low in the Netherlands (median, 20.8 g/d among adults),[49] which was reflected by only 9% of patients in the present study adhering to national recommendations.

The mechanisms by which fiber intake might be associated with postoperative complications are unclear, although the classical role of fiber in maintaining gut health is considered plausible.[50] The intestinal microbiota reflects an aspect of gut health that has been suggested to impact postoperative

Table 1. Characteristics of the Study Population by Occurrence of Postoperative Complications

| Characteristic | Patients[a] | | |
|---|---|---|---|
| | | Any postoperative complication (n = 1399) | |
| | Overall (N = 1399) | Yes (n = 397 [28%]) | No (n = 1002 [72%]) |
| Age, median (IQR), y | 66 (61-72) | 67 (62-73) | 66 (61-71) |
| Sex | | | |
| Male | 896 (64) | 279 (70) | 617 (62) |
| Female | 503 (36) | 118 (30) | 385 (38) |
| BMI, median (IQR)[b] | 26.0 (24.0-28.7) | 26.5 (24.0-29.1) | 25.9 (23.9-28.7) |
| Smoking | | | |
| Current | 151 (11) | 63 (16) | 88 (9) |
| Former | 818 (59) | 220 (56) | 598 (60) |
| Never | 424 (30) | 113 (29) | 311 (31) |
| Unknown | 6 (0.4) | 1 (0.2) | 5 (0.5) |
| Adhered to recommendation for dietary fiber intake[c] | 125 (9) | 34 (9) | 91 (9) |
| Dietary fiber intake, median (IQR), g/d | | | |
| Total dietary fiber | 19.6 (15.8-24.2) | 18.8 (15.2-23.2) | 20.1 (16.1-24.5) |
| Cereal fiber | 8.9 (6.7-11.3) | 8.6 (6.4-10.9) | 9.1 (6.8-11.5) |
| Whole grain fiber | 6.8 (4.7-9.0) | 6.5 (4.4-8.8) | 6.9 (4.8-9.1) |
| Refined grain fiber | 1.8 (1.0-3.0) | 1.7 (1.0-2.8) | 1.9 (1.1-3.0) |
| Fruit fiber | 2.6 (1.3-3.9) | 2.1 (1.2-3.8) | 2.7 (1.3-4.0) |
| Vegetable fiber | 2.3 (1.4-3.3) | 2.1 (1.2-3.0) | 2.4 (1.5-3.4) |
| Energy intake, median (IQR), kcal/d | 1819 (1503-2169) | 1791 (1470-2143) | 1822 (1508-2185) |
| Moderate to vigorous physical activity, median (IQR), min/wk[d] | 660 (330-1140) | 600 (300-1100) | 690 (330-1170) |
| Tumor location[e] | | | |
| Colon | 956 (68) | 225 (57) | 731 (73) |
| Rectum | 443 (32) | 172 (43) | 271 (27) |
| Tumor stage | | | |
| I | 345 (25) | 83 (21) | 262 (26) |
| II | 381 (27) | 113 (29) | 268 (27) |
| III | 586 (42) | 179 (45) | 407 (41) |
| IV | 79 (6) | 21 (5) | 58 (6) |
| Unknown | 8 | 1 | 7 |
| Received neoadjuvant radiotherapy and/or chemotherapy | 335 (24) | 134 (34) | 201 (20) |
| ASA classification | | | |
| I | 414 (30) | 83 (22) | 331 (34) |
| II | 793 (58) | 228 (59) | 565 (57) |
| III | 161 (12) | 73 (19) | 88 (9) |
| IV | 3 (0.2) | 2 (0.5) | 1 (0.1) |
| Unknown | 28 | 11 | 17 |
| Surgical approach | | | |
| Open | 350 (25) | 115 (30) | 235 (24) |
| Laparoscopic | 1032 (75) | 274 (70) | 758 (76) |
| Unknown | 17 | 8 | 9 |
| Anastomosis[f] | 1250 (90) | 342 (87) | 908 (91) |
| Stoma[g] | 399 (29) | 170 (44) | 229 (23) |
| Admitted to intensive care unit for at least 1 d[h] | 105 (8) | 88 (23) | 17 (2) |
| Length of hospital stay, median (IQR), d[i] | 6 (4-9) | 11 (7-18) | 5 (4-7) |

Abbreviations: ASA, American Association of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Data were missing for 5 patients.

[c] The recommendation for dietary fiber intake in the Netherlands according to the Health Council is at least 3.4 g/MJ per day, including approximately 30 g per day for women and approximately 40 g per day for men.[45]

[d] Data were missing for 2 patients.

[e] Colon includes the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, and sigmoid colon. Rectum includes the rectosigmoid junction and rectum.

[f] Data were missing for 3 patients.

[g] Refers to both defunctioning stomas and permanent end stomas created during surgery. Data were missing for 20 patients.

[h] Data were missing for 10 patients.

[i] Data were missing for 285 patients.

recovery and risk of complications and might mediate the observed associations for fiber intake.[16,24,51-53]

We observed an association between fiber intake and risk of complications among women but not among men, although there was no significant interaction between sex and dietary fiber intake. In rodent models,[40,41] dietary fiber intake affected microbiota composition, SCFA production, and immune parameters in a sex-specific manner. Several, albeit

Table 2. Association Between Habitual Dietary Fiber Intake Before Surgery and Postoperative Complications

| | Dietary fiber intake, median (IQR), g/d | Crude model[a] | | Adjusted model[b] | |
|---|---|---|---|---|---|
| | | Events, No./ total population, No. | OR (95% CI) | Events, No./ total population, No. | OR (95% CI) |
| **Any complications** | | | | | |
| Dietary fiber intake, per 10 g/d | 19.6 (15.8-24.2) | 397/1399 | 0.74 (0.61-0.89) | 385/1365 | 0.75 (0.62-0.92) |
| Dietary fiber intake | | | | | |
| Tertile 1 | 14.4 (12.2-15.8) | 151/466 | 1 [Reference] | 148/457 | 1 [Reference] |
| Tertile 2 | 19.6 (18.4-21.0) | 129/467 | 0.78 (0.59-1.03) | 123/452 | 0.76 (0.56-1.02) |
| Tertile 3 | 26.1 (24.1-29.5) | 117/466 | 0.69 (0.52-0.92) | 114/456 | 0.72 (0.53-0.98) |
| *P* value for trend | NA | NA | .01 | NA | .04 |
| **Surgical complications** | | | | | |
| Dietary fiber intake, per 10 g/d | 19.7 (15.8-24.2) | 235/1387 | 0.76 (0.60-0.95) | 231/1354 | 0.76 (0.60-0.97) |
| Dietary fiber intake | | | | | |
| Tertile 1 | 14.4 (12.2-15.8) | 89/463 | 1 [Reference] | 89/454 | 1 [Reference] |
| Tertile 2 | 19.7 (18.4-21.0) | 81/461 | 0.89 (0.63-1.24) | 78/447 | 0.85 (0.61-1.20) |
| Tertile 3 | 26.1 (24.2-29.5) | 65/463 | 0.68 (0.47-0.96) | 64/453 | 0.69 (0.48-0.98) |
| *P* value for trend | NA | NA | .03 | NA | .04 |
| **Anastomotic leakage[c]** | | | | | |
| Dietary fiber intake, per 10 g/d | 19.6 (15.7-24.3) | 67/1237 | 0.91 (0.62-1.33) | 65/1208 | 0.97 (0.66-1.43) |
| Dietary fiber intake | | | | | |
| Tertile 1 | 14.2 (11.9-15.7) | 23/414 | 1 [Reference] | 23/406 | 1 [Reference] |
| Tertile 2 | 19.6 (18.3-21.0) | 22/410 | 0.95 (0.52-1.73) | 20/397 | 0.92 (0.49-1.72) |
| Tertile 3 | 26.1 (24.2-29.5) | 22/413 | 0.86 (0.47-1.58) | 22/405 | 0.95 (0.51-1.77) |
| *P* value for trend | NA | NA | .62 | NA | .89 |

Abbreviations: IQR, interquartile range; NA, not applicable; OR, odds ratio.

[a] The crude model was adjusted for age (continuous in years) and sex.

[b] The adjusted model was adjusted for age, sex, smoking status (former, current, or never), American Association of Anesthesiologists classification (I, II, or III-IV), and tumor location (colon, rectum).

[c] Analyses were restricted to patients with an anastomosis.

Table 3. Stratified Analyses for the Association Between Dietary Fiber Intake and Any Postoperative Complications

| Stratified analysis | Dietary fiber intake, median (IQR), g/d | Adjusted model[a] | |
|---|---|---|---|
| | | Events, No./ total population, No. | OR (95% CI) |
| **Sex** | | | |
| Dietary fiber intake, per 10 g/d | | | |
| Women | 18.8 (15.2-22.9) | 116/497 | 0.64 (0.44-0.94) |
| Men | 20.2 (16.2-24.8) | 269/868 | 0.79 (0.63-1.01) |
| **Tumor location** | | | |
| Dietary fiber intake, per 10 g/d | | | |
| Colon[b] | 19.8 (15.8-24.2) | 219/929 | 0.78 (0.61-1.01) |
| Rectum[c] | 19.4 (15.7-23.8) | 166/436 | 0.71 (0.51-0.98) |

Abbreviations: IQR, interquartile range; OR, odds ratio.

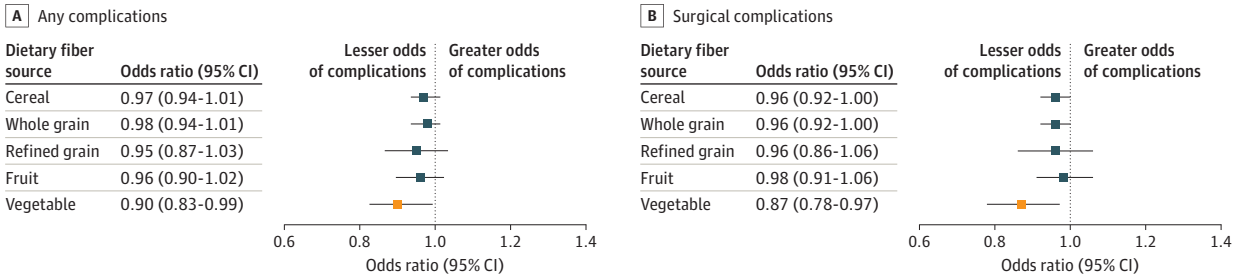
[a] Models were adjusted for age at inclusion, sex (not in analyses stratified for sex), smoking status (former, current, or never), American Association of Anesthesiologists classification (I, II, or III-IV), and tumor location (colon, rectum; not in analyses stratified for tumor location).

[b] Colon includes the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, and sigmoid colon.

[c] Rectum includes the rectosigmoid junction and rectum.

speculative, hypotheses might explain our findings. Higher fiber intake has been associated with a reduction in circulating estrogen concentrations and increased fecal excretion of estrogens in human and animal studies.[54-56] Dietary fiber can bind estrogens released from the bile in the gastrointestinal tract and thereby can prevent reabsorption through interruption of the enterohepatic circulation.[57] Although the biological and clinical significance of this phenomenon is unknown, studies have shown that estrogens might promote wound healing and improve perfusion.[58-60] Another explanation might be that, in general, women tend to consume relatively more fruits and vegetables and fewer cereals or cereal products compared with men.[61,62] Dietary fiber from these respective sources may differ in terms of solubility, fermentability, or viscosity and, as such, may have different bulking effects, bacterial fermentation, or absorptive capacity in the colon.[63,64] The observa-

Figure 2. Associations Between Fiber Intake From Different Sources and Risk of Postoperative Complications




Analyses were adjusted for age, sex, smoking status, American Association of Anesthesiologists classification, and tumor location and were mutually adjusted for dietary fiber intake of other sources. Cereal fiber was further adjusted for fruit fiber and vegetable fiber. Whole grain fiber was further adjusted for refined grain fiber, fruit fiber, and vegetable fiber. Refined grain fiber was further adjusted for whole grain fiber, fruit fiber, and vegetable fiber. Fruit fiber was further adjusted for vegetable fiber, whole grain fiber, and refined grain fiber. Vegetable fiber was further adjusted for fruit fiber, whole grain fiber, and refined grain fiber. Markers indicate odds ratios per 1 g per day increase in fiber intake, with horizontal lines indicating 95% CIs.

tion for which we found the strongest associations for fiber from vegetables is supportive of this hypothesis.

We found no significant associations between fiber intake and risk of anastomotic leakage. These findings contradict a previous preclinical study[65] showing that a high-fiber and low-fat diet resulted in a decreased risk of anastomotic leakage compared with a Western-style diet (low fiber and high fat). Whether effects in this animal study were attributed to dietary fiber, fat, or both is unknown, which together with the Western-style diet lacking dietary fiber[65] rather than a modest fiber intake seen in human populations, might explain differences with our findings. In addition, the relatively low proportion (5%) of patients with anastomotic leakage might explain failure to detect an association in our study.

### Strengths and Limitations

Strengths of this study include the prospective design and timing of exposure assessment, which is relevant from a prehabilitation point of view. Moreover, to our knowledge, this was the first study specifically focusing on habitual fiber intake in association with complications after surgical treatment for CRC that considered a comprehensive panel of dietary, other lifestyle, and clinical factors.

Limitations of this study include the modest number of events, especially for surgical complications and anastomotic leakage, which limited statistical power to conduct stratified and sensitivity analyses for these outcomes. In line with this and given the nature of the data, we were not able to differentiate between specific types of surgical complications other than anastomotic leakage. Second, we focused on habitual dietary fiber intake reflecting the 4 weeks before diagnosis. Patients might have changed their dietary habits after diagnosis and before the surgical procedure, although a previous study[66] on lifestyle changes after diagnosis in this cohort revealed that this was likely not the case. Because the median time between completion of the FFQ and surgery was only 8 days (IQR, 2-17 days), it is not likely that changes in dietary fiber intake substantially impacted our findings. Third, for some patients, data on the exposure (fiber intake, n = 125) or the outcome (complications, n = 70) were missing. These patients, however, did not differ substantially from the study population in terms of sociodemographic characteristics and cancer stage. In addition, although we carefully considered multiple clinical, nutritional, and other lifestyle factors, we cannot exclude the possibility of residual confounding inherent to the observational design of our study. Of note, energy adjustment using the residual method[44] resulted in slight attenuation of observed associations in terms of statistical significance, although effect estimates remained similar compared with the main analyses. This phenomenon has also been observed in other studies focusing on dietary fiber.[67] The wider 95% CIs calculated after energy adjustment may reflect overadjustment or unnecessary adjustment.[67,68] From a biological point of view, we consider absolute dietary fiber more relevant than relative intake because the actual amount of fiber passing through the gastrointestinal tract might be more important with regard to biological events. For these reasons, we primarily based our conclusions on the non-energy-adjusted models.

## Conclusions

In this cohort study, higher dietary fiber intake before surgery was associated with a lower risk of any or surgical postoperative complications in patients with CRC. The findings suggest that improving preoperative dietary fiber intake may be considered in future prehabilitation programs for patients undergoing surgery for CRC. Further intervention studies appear to be needed to confirm the feasibility and clinical relevance of increased dietary fiber intake in the time between diagnosis and the surgical procedure.

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