# Insights into Food Intake, Overall Diet Quality, and Stool Short-Chain Fatty Acids during Treatment for Rectal Cancer: A Pilot Study

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**Objective**: To describe food intake and overall diet quality during neoadjuvant concomitant chemotherapy and radiation therapy (nCRT) for rectal cancer. We also explored associations between Prime Diet Quality Score (PDQS) and short-chain fatty acid (SCFA) levels in stool at the end of nCRT in a subset of participants.

**Methods**: Thirty-two participants provided a 24-hour dietary recall, while 18 provided stool samples for SCFA analysis.

**Results**: The reported intake of 11 healthy food groups (e.g., dark green vegetables, fish) was low (<50% of participants) before treatment, while 4 unhealthy food groups (e.g., processed meat, sugar-sweetened beverages) were high (>50%), both before and after treatment. Higher propionate levels were associated with higher PDQS values.

**Conclusion**: Participants reported reduced dietary intake and diet quality during nCRT. Additional study is warranted to determine whether gut metabolites may mediate the impact of low diet quality.

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*Key words: Diet quality, Rectal cancer, Stool short chain fatty acids*

While data on dietary factors associated with the risk of developing colorectal cancer (CRC) and mortality exist (1), evidence on both dietary intake and diet quality, especially during the phase of rectal cancer (RC) treatment, is scarce. Importantly, the American Cancer Society (ACS) dietary guidelines recommend a plant-based diet with low to no intake of red and processed meats, sugar-sweetened beverages, highly processed foods, and refined grain products (2). In addition to the well-known benefits of good nutrition during cancer treatment, such as ameliorating side-effects, maintaining strength and energy, weight maintenance, and lowering risk of infections, dietary intake and diet quality have vital roles in the maintenance of gut homeostasis. Adequate dietary intake and diet quality may also contribute to fewer treatment-related gastrointestinal (GI) effects and better health-related quality of life (QOL) (3,4).

Both low diet quality (5) and environmental factors, such as cancer treatments, are likely to affect gut microbial composition and function, impacting the production of important microbial-derived metabolites such as short-chain fatty acids (SCFAs) (6). These SCFAs (e.g., acetate, propionate, butyrate, representing 90%–95% of the SCFAs present in the colon) are produced by the microbial fermentation of undigested carbohydrates and dietary fiber. They are believed to have critical roles in regulating gut inflammation and homeostasis, as well as distinct functional impacts on host regulatory immune responses (7). Among breast cancer patients, increased propionate and acetate levels after 3 cycles of chemotherapy have been observed (8), while other investigators have reported decreased butyrate and iso/valerate levels associated with fatigue in head and neck cancer patients (9).

Given the importance of maintaining a high-quality diet during cancer treatment, this pilot study was designed to describe food intake and overall diet quality during neoadjuvant concomitant chemotherapy and radiation therapy (nCRT) for RC using the Prime Diet Quality Score (PDQS) (10,11). Associations between PDQS values and SCFA levels at the end of nCRT for a subset of RC participants were also evaluated. This study's preliminary findings will inform further rigorous study of these factors, particularly in identifying high-risk dietary patterns and biologically relevant therapeutic targets that may aid in reducing nCRT-related side-effects and improve outcomes in the RC population.

## Methods

### Study population

Patients eligible for inclusion were men and women aged > 18 years, scheduled to receive nCRT for locally advanced RC, and able to provide written informed consent. We excluded patients with extreme diets (e.g., parenteral nutrition), a history of inflammatory or infectious conditions, or diagnosed psychiatric disorders, as well as those who had used antibiotics, probiotics, or prebiotics

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within the month prior to sample collection. The study took place in South Florida from September 2017 through April 2019. Ethical approval for the study was provided by the Southeastern Academic Medical Center.

### Measures

Participants underwent 2 assessments (before and at the end of nCRT) during which said participants completed self-reported questionnaires and provided stool samples at the end of nCRT. Common demographics and clinical and treatment characteristics were collected. Dietary intake, assessed using a 24-hour food recall at each time point, was used to derive the PDQS-24HR for diet quality (10,11). We employed the dichotomous scoring approach described previously (10). We grouped individual food items into the 14 healthy food groups (containing, for example, dark green vegetables) and 7 unhealthy food groups (containing, for example, processed meat) in the PDQS

Stool samples (50 mg) collected from participants were shipped to the Duke Proteomics/Metabolomics Shared Resource Lab for the measurement of acetic, propionic, and butyric SCFAs using ultra-performance liquid chromatography–mass spectrometry. The typical concentration range detected with this method is 0.1–200 μM (nmol/mg); the results were log2-transformed.

### Statistical analysis

Descriptive statistics including percentages, means, and standard deviations were summarized for demographic, clinical, and dietary data. A paired-samples t-test was used to compare mean PDQS values before and at the end of treatment. In a subset of 18 participants who provided stool samples at the end of nCRT, we examined associations between end-of-treatment PDQS and SCFA concentration using Pearson correlations. Statistical analyses were performed using R, version 4.1.2.

## Results

The entire sample (n = 32; 17 women) received the same nCRT regimen of standard radiation therapy delivered at doses of 1.8 Gy, 5 days per week, to a total of 50.4 Gy, with concurrent 5-fluorouracil infusion or oral capecitabine for 5 weeks (Table 1). Individual food-group intake (measured by the PDQS) before and after nCRT for each participant is presented in Table 2. The mean PDQS was lower at the end of nCRT than it was before treatment; however, this difference was not statistically significant (Table 2). At the end of treatment, there was a trend toward elevated propionic acid levels associated with higher PDQS values (P = .058).

**Table 1**. Study participants' demographic and clinical characteristics

| | Overall (N = 32) |
|---|---|
| Age, M (SD) | 57.97 (11.22) |
| Sex, N (%) | |
| Female | 17 (53%) |
| Male | 15 (47%) |
| Ethnicity, N (%) | |
| White/non-Hispanic | 23 (72%) |
| White/Hispanic | 5 (16%) |
| Black/non-Hispanic | 2 (6.3%) |
| Asian | 1 (3.1%) |
| Other | 1 (3.1%) |
| Marital status[1], N (%) | |
| Married | 20 (65%) |
| Single | 2 (6.5%) |
| Widowed | 1 (3.2%) |
| Divorced | 6 (19%) |
| Living with partner | 1 (3.2%) |
| Other | 1 (3.2%) |
| Job status[2], N (%) | |
| Incapacitated | 2 (6.9%) |
| Not working | 6 (21%) |
| Retired | 10 (34%) |
| Working | 11 (38%) |
| Years in school[1], M (SD) | 13.36 (3.05) |
| BMI[3], M (SD) | 28.05 (7.53) |
| Hgb[4], M (SD) | 12.04 (2.04) |
| Stage[1], N (%) | |
| I | 2 (6.5%) |
| II | 4 (13%) |
| III | 21 (68%) |
| IV | 4 (13%) |
| Chemotherapy treatment, N (%) | |
| 5-Fluorouracil infusion | 18 (56%) |
| Oral capecitabine | 14 (44%) |

Abbreviations: BMI, body mass index; Hgb, hemoglobin; M, mean; N, number; SD, standard deviation.
NB: Continuous variables are summarized as mean ± standard deviation. Categorical variables are summarized with frequencies and percentages.
[1]Missing data for 1 participant.
[2]Missing data for 3 participants.
[3]BMI, missing data for 4 participants.
[4]Hgb, missing data for 8 participants.

## Discussion

This pilot study explored dietary intake and diet quality during nCRT for RC and their associations with SCFA levels. The participants' mean PDQS values both before and after treatment were, on average, lower than the midpoint of the scale (<10.5), suggesting that diet quality needed improvement even before treatment. Low diet quality during cancer treatment can lead to increased risk of infection, malnutrition, and compromised chemotherapy effectiveness in animal models (12–14). While associations with diet quality and patient-reported outcomes were not evaluated in the present study, studies conducted in populations with other cancer types indicate that after treatment, higher diet quality is associated with better physical functioning and self-rated health, as well as a decreased risk of depression (12,15).

Fewer than 50% of the participants reported consuming each of 11 of the 14 healthy food groups before and after treatment. This finding is important because it suggests that RC patients may commonly have an inadequate intake of essential nutrients and other dietary components associated with good health and anti-inflammatory properties (e.g., fibers, folate, iron, vitamins A and C)

**Table 2**. Prime diet quality score and individual food group intake before and after neoadjuvant concomitant chemotherapy and radiation therapy

| | Before nCRT N = 32 | After nCRT N = 32 |
|---|---|---|
| Healthy food groups, N (%)[1] | | |
| Dark green vegetables | 14 (43.8) | 10 (31.3) |
| Cruciferous vegetables | 7 (21.9) | 4 (12.5) |
| Deep orange vegetables & other vitamin A–rich vegetables | 4 (12.5) | 4 (12.5) |
| White roots/tubers | 21 (65.6) | 21 (65.6) |
| Other vegetables | 18 (56.3) | 18 (56.3) |
| Citrus fruits | 2 (6.3) | 1 (3.1) |
| Deep orange fruits | 2 (6.3) | 2 (6.3) |
| Other fruits | 8 (25.0) | 8 (25.0) |
| Beans, peas, soy products | 6 (18.8) | 7 (21.9) |
| Nuts, seeds | 4 (12.5) | 0 (0.0) |
| Poultry | 16 (50.0) | 16 (50.0) |
| Fish | 3 (9.4) | 3 (9.4) |
| Low-fat dairy | 5 (15.6) | 7 (21.9) |
| Whole grains | 21 (65.6) | 11 (34.4) |
| Vegetable oils | 1 (3.1) | 5 (15.6) |
| Neutral food group, N (%)[1] | | |
| Eggs | 5 (15.6) | 4 (12.5) |
| Unhealthy food groups, N (%)[1] | | |
| Red meat | 16 (50.0) | 15 (46.9) |
| Processed meat | 18 (56.3) | 20 (62.5) |
| Refined grains, baked products | 21 (65.6) | 11 (34.4) |
| Sugar-sweetened beverages | 20 (62.5) | 19 (59.4) |
| Desserts and ice cream | 22 (68.8) | 24 (75.0) |
| Fried food not from home | 26 (81.3) | 17 (53.1) |
| Overall diet quality, M (SD) | | |
| PDQS[2] total score | 7.53 (2.24) | 6.84 (2.34) |

Abbreviations: nCRT, neoadjuvant concomitant chemotherapy and radiation therapy; PDQS, Prime Diet Quality Score; SD.
[1]Data are presented as N (%) of participants consuming >1 serving/day for individual food groups.
[2]PDQS ranges from 0–50, with higher scores indicating better diet quality (P = .688 by paired t-test).

(11). A recent literature review found that the high consumption of fiber (i.e., whole grain cereals, green and cruciferous vegetables) was associated with lower cancer-associated mortality (16). It is important to mention that the data for this study were collected on site during outpatient radiotherapy visits, and patients received formal nutritional assessment and education only if the attending physician initiated a dietician consultation. None of our participants reported receiving a formal dietitian consultation during the study period, suggesting that it is possible that their low intake of healthy foods was related to limited nutrition knowledge. In a prior study, researchers found that a 12-month lifestyle-modification program that included a Mediterranean diet, exercise, and vitamin D led to improvements in QOL and breast cancer-related symptoms (17). Similar findings have been reported among CRC survivors (18). Since diet is an important modifiable determinant of human health, more research on nutrition knowledge and on interventions in cancer populations is warranted to inform dietary choices (19) in cancer patients. Although not evaluated in the present study, it is possible that low diet quality was a nutrition-related nCRT side-effect. Indeed, literature reviews and meta-analyses suggest that up to 86% of patients undergoing chemotherapy (including 5-fluouracil to treat RC) may experience taste and smell alterations and GI side effects (e.g., grade 3–4 diarrhea) (20–22). Such alterations may result in reduced food enjoyment, potentially leading to inadequate food intake (23,24), thereby placing these patients at risk for low diet quality. In our current studies with RC patients, we are collecting more robust GI-symptom data using the Patient-Reported Outcomes Measurement Information System (e.g., subscales for diarrhea; bowel incontinence/soilage; nausea, vomiting, and poor appetite; and constipation). Investigating the long-term impacts of nCRT on gut-derived metabolites and on GI-symptom burden is particularly important for patients with RC and may help elucidate the underlying biological mechanisms driving these long-term morbidities.

The finding that unhealthy foods were consumed by most of the participants both before and after treatment was unexpected. While 1 study of CRC patients found that the consistent high intake (before and after diagnosis) of red and processed meat was associated with a higher risk of cancer-specific mortality (25), other studies have not (26). As noted, it is possible that the high intake of unhealthy food groups is related to nutrition-related nCRT side-effects. For example, some chemotherapies may cause food to taste different for cancer patients (e.g., to have a bitter or metallic taste).

**Table 3**. Pearson correlations between short-chain fatty acids and prime diet quality score at the end of neoadjuvant concomitant chemotherapy and radiation therapy (n = 18)

| Variable | Mean (SD) | Correlation with PDQS[1] | *P* value |
|---|---|---|---|
| PDQS total score | 7.33 (2.30) | 1.00 | — |
| Short-chain fatty acids, nmol/mg[2] | | | |
| Acetic acid | 4.73 (0.95) | 0.20 | .432 |
| Propionic acid | 2.81 (0.66) | 0.46 | .058 |
| Butyric acid | 1.43 (0.92) | −0.15 | .557 |

Abbreviation: SCFA, short-chain fatty acid.
NB: Data are presented as mean (SD). Correlation analysis based on n = 18 participants with available stool samples for SCFA measurement.
[1]PDQS ranges from 0–50, with higher scores indicating better diet quality.
[2]SCFA concentrations were log2-transformed prior to correlation analysis.

Ideal diets (e.g., a high intake of vegetables, legumes, and nuts) are often not tolerated during radiation treatment, and certain "unhealthy" foods may be tastier (e.g., sweetened beverages, sugary desserts, fried foods, and heavily processed snacks such as potato chips or sugary cereals) and so preferred (27). Additionally, a recent literature review concluded that none of the unhealthy food categories should be completely eliminated but rather consumed in moderation (16). An important gap that warrants examination in future studies is the limited understanding of the effects that factors such as socioeconomical status, food security, and dietary acculturation might have on dietary intake and diet quality. For example, 1 study found that low social class, low education, and difficulty paying bills were associated with lower fruit and vegetable variety (28).

We further identified a potential trend for a positive correlation between propionic acid (one of the SCFAs examined) and end-of-treatment diet quality (PDQS). Similarly, higher levels of stool acetic and propionic acids were positively associated with diet quality indices in subjects with chronic diseases (29) as well as in healthy volunteers (5). The potential underlying mechanisms behind the interaction of diet, the gut microbiota, and host regulatory immune responses have been the subject of numerous extensive reviews (30,31). One plausible explanation proposes that the availability of microbial-derived SCFAs in the gut is likely influenced by environmental factors such as dietary habits (e.g., the intake of fiber) and medications (e.g., antibiotics, chemotherapeutic agents), which together contribute to shaping the diversity and metabolism of the microbiota (32). These SCFAs play a pivotal role in maintaining homeostasis in humans (30,31). In fact, SCFAs have a range of functions both in the gut and peripherally, with differences in local and systemic effects governed by their availability. For example, butyrate is important in stabilizing gut epithelial barrier function via the consumption of local oxygen molecules and subsequent stabilization of the barrier that protects the transcription factor hypoxia-inducible factor (32). Thus, the nCRT-induced lowering of SCFA levels may lead to increased intestinal permeability and the translocation of bacteria associated with a systemic inflammatory cascade that may compromise host regulatory immune responses. Further, identifying a type of diet that can modulate SCFA synthesis and/or the abundance of SCFA-synthesizing bacteria may be clinically relevant. There is some evidence that a Mediterranean diet, characterized by high intakes of fiber-rich plant foods, olive oil, and seafood, is associated with higher levels of SCFAs in stool and inversely associated with intestinal permeability biomarkers (e.g., lipopolysaccharide-binding protein in plasma and zonulin in stool) (33). As this topic moves into larger longitudinal studies, it is crucial to evaluate the effects of nCRT on SCFAs and on sources of gut variability—including modifiable factors such as diet—that may impact host regulatory immune responses associated with treatment outcomes.

### Limitations

Our results should be carefully considered because of the study's inherent limitations. The sample size was small (32 participants provided a 24-hour dietary recall, while 18 provided stool samples for SCFAs), which limited our ability to stratify data (e.g., by demographic or clinical variables) and pursue further inferential statistics due to small cell sizes. Another important limitation is that diet quality was evaluated using a PDQS based on a single 24-hour dietary recall. We acknowledge that the PDQS was developed to serve as a simple tool to evaluate the association between diet quality and the risk of cardiovascular diseases (10), and has yet to be validated in an RC population. However, the PDQS has been used to evaluate diet quality and related-health outcomes in patients with other chronic conditions. For example, the PDQS was inversely associated with risk of irritable bowel syndrome (34) and of depression and anxiety in adults (35). In addition, using data from the US National Health and Nutrition Examination Survey, researchers found that the PDQS values and Healthy Eating Index (HEI)–2015 scores (derived using 24-hour recalls) were associated with mortality risk in the US population (36). Validation of the findings in a larger, well-controlled longitudinal study to permit the evaluation of more broadly used dietary indices (i.e., HEI-2020, the alternate Mediterranean Diet score, an ACS dietary index) is warranted. Such validation could be explored using the food frequency questionnaire validated among cancer patients (37) or the average of 3 24-hour food recalls at each time point. The increasingly prevalent dietary preferences of intermittent fasting and ketogenic diets, which have been associated with breast cancer treatment effectiveness, improved QOL, and more favorable illness perception, also warrant evaluation in relation to dietary intake and diet quality. Lastly, validation of the associations between SCFAs and diet quality is also warranted.

## Resumen

Objetivo: Describir la ingesta de alimentos y la calidad general de la dieta durante la quimio-radioterapia concurrente (nCRT, por sus siglas en inglés) para el cáncer de recto. También exploramos las asociaciones entre el Prime Diet Quality Score (PDQS) y los niveles de ácidos grasos de cadena corta (SCFA, por sus siglas en inglés) en heces al final de nCRT en un subgrupo de participantes. Métodos: Treinta y dos participantes proporcionaron un registro dietético de 24 horas, mientras que 18 proporcionaron muestras de heces para los SCFA. Resultados: La ingesta informada de 11 grupos de alimentos saludables (p. ej., verduras de color verde oscuro, pescado) fue baja (<50% de los participantes) antes del tratamiento, mientras que 4 grupos de alimentos no saludables (p. ej., carne procesada, bebidas azucaradas) fueron altos (>50%) tanto antes como después del tratamiento. Niveles altos de propionato se asociaron con una puntuación de PDQS más alta. Conclusión: Los participantes informaron una menor ingesta y calidad de la dieta durante el tratamiento con nCRT. Se justifica realizar estudios adicionales para comprender si los metabolitos intestinales pueden mediar el impacto de la baja calidad de la dieta.

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## Conclusion

Patients with RC may experience lower quality dietary intake following nCRT. This potential deficiency may be mitigated by interventions designed to improve dietary intake and overall diet quality during nCRT. In a future study, we aim to follow a large prospective cohort of RC patients undergoing nCRT to examine the relationships between dietary intake and diet quality and differences in stool SCFA levels. Doing so may provide an opportunity to identify specific dietary patterns and components that influence microbial metabolism and potentially impact downstream health-related outcomes.

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