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Dietary changes impact the gut microbe composition in overweight and obese men with prostate cancer undergoing radical prostatectomy

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Abstract

Background—Diet and obesity influence prostate cancer risk and progression–effects that may be mediated through the gut microbiome.

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Disclosure
No authors report a conflict of interest.

Objective—Explore relationships between diet, gut microbes and Gleason sum in overweight and obese prostate cancer patients enrolled in a presurgical weight loss trial.

Design—Randomized Controlled Trial (NCT01886677) secondary analysis.

Participants/setting—In 2013–2014, 40 prostate cancer patients in the southeastern United States were randomized and equally allocated to weight loss and wait-list control arms while they awaited prostatectomy; stool samples were collected on a subset of 22.

Intervention—Registered dietitians and exercise physiologists provided semi-weekly in-person and telephone-based guidance on calorie-restricted diets and exercise to promote ~0.91 kg/week weight loss.

Main outcome measures—Baseline and follow-up 24-hour dietary recalls were conducted and analyzed (ASA24) for macronutrients, micronutrients, and food groups. Microbiome analysis targeting the V4 region of the 16S rRNA gene was performed on fecal samples. Biopsy Gleason sum data were accessed from diagnostic pathology reports.

Statistical analyses performed—Associations between dietary factors and operational taxonomic units (OTUs) were determined by beta diversity analysis. Wilcoxon Signed Rank and Mann-Whitney U-testing assessed within- and between- arm differences. Associations between Gleason sum and OTUs, and diet and OTUs, were analyzed using Spearman correlations.

Results—At baseline, Proteobacteria (median: 0.06, interquartile range: 0.01–0.16) were abundant, with four orders positively associated with Gleason sum. Gleason sum was associated with *Clostridium* (ρ= 0.579, p=0.005) and *Blautia* (ρ= −0.425, p=0.049). Increased red meat consumption from baseline was associated with *Prevotella* (ρ= −0.497, p=0.018) and *Blautia* (ρ= 0.422, p=0.039). Men who increased poultry intake had decreased Clostridiales abundance (p=0.009).

Conclusions—This hypothesis-generating study provides a starting point for investigating the relationships between the fecal microbiome, diet and prostate cancer. Adequately powered studies are required to further explore and validate these findings.

Keywords

Prostatic neoplasms; gastrointestinal microbiome; microbiota; weight loss; diet; obesity; Proteobacteria

Introduction

Obesity is a risk factor for several types of cancer and has been associated with more aggressive disease and poor outcomes in prostate cancer.[1, 2] It is hypothesized that weight loss could be an effective preventive measure for obesity-associated cancers.[3] Recently there has been conjecture regarding the role of the gut microbiome in potentially mediating the impact of negative energy balance.

The human digestive tract is inhabited by thirty to forty trillion bacteria and other single cell organisms.[4] These organisms are integral in fermenting unabsorbed macronutrients into beneficial short chain fatty acids and vitamins that can be absorbed and utilized by the host.

[5, 6] Because the microbiome is a dynamic ecosystem containing thousands of taxa with unique metabolic processes and behaviors, it is important to characterize the microbiome in host disease states, as has been documented in obesity,[7–10] metabolic syndrome,[11] diabetes,[12, 13] colorectal cancer,[14, 15] and breast cancer.[16] Longitudinal studies have been proposed to describe a microbiota composition that may precede diseases such as prostate cancer, hypothesizing that the effects of dietary factors and subsequent changes in the microbiome composition could prevent disease onset and/or progression.[17]

The concept of dysbiosis, or an unstable microbial community, has been hypothesized to contribute to chronic diseases through several mechanisms.[18] Though the human gut harbors pathogens and responds rapidly to them as in the case of food poisoning, it is possible that non-pathogenic bacteria may be deleterious to community homeostasis.[19] The inflammation associated with dysbiosis can manifest locally as in gastrointestinal diseases, but also results in intestinal permeability which can allow dietary nutrients and bacterial metabolites to enter the circulatory system.[20]

While diet is known to affect various hormones and metabolic pathways, the relationship between diet and the microbiome has yet to be fully understood. Short-term dietary changes have been shown to cause significant shifts in microbiome composition;[21–25] however, many artifacts from mode of birth and breastfeeding in infancy,[26] frequency and latency of antibiotic use,[27] habitual diet,[28] and other factors prevent characterization of a single healthy or ideal microbiome.[29] More evidence is needed to establish desirable levels of various bacterial species and further characterize diets that could potentially promote and/or maintain that balance. It is unknown whether a signature of fecal microbiota exists in prostate cancer as has been observed in colorectal cancer.[30]

The objectives of this study were to describe the microbiota in men with clinically-confirmed prostate cancer and to investigate the longitudinal relationships between weight, dietary factors and microbiota during a presurgical weight loss trial conducted at The University of Alabama at Birmingham from 2013 to 2014.

Subjects and Methods

Participants in this study were men with prostate cancer enrolled in a presurgical weight loss trial (NCT01886677) approved by the Institutional Review Board of the University of Alabama at Birmingham (UAB), and described previously.[31] Forty men were recruited through the urology clinics at UAB and the Urology Centers of Alabama from 2013 to 2014. Microbiome analysis became available midway through the trial; the remaining subset of 22 men who had complete diet and microbiome data at baseline and follow-up visits were included in this secondary analysis. Study participants had to be overweight or obese (BMI≥25 kg/m^2), have no medical conditions that would affect weight status or the ability to pursue unsupervised exercise, received no other treatment for their prostate cancer, and scheduled for surgery at least 23 days after study enrollment and their baseline appointment. All participants provided written informed consent.

After completing baseline appointments, men were randomized to either weight loss or wait-list control conditions and completed follow-up visits 1–2 days prior to surgery. Men randomized to the weight loss arm were prescribed a healthful energy-restricted diet and encouraged to exercise 30 minutes/day to promote weight loss of 0.91 kilograms per week. Diet and exercise guidance was provided through semi-weekly in-person and telephone contact with a registered dietitian and an exercise physiologist. Men in the control arm were offered the intervention after prostatectomy. All medications were recorded at baseline and follow-up appointments.[32, 33] Two-24 hour dietary recalls (one weekend and one week day) were obtained by a registered dietitian using a multiple pass method at baseline and follow-up and entered into the ASA24 (2011. Bethesda, MD: National Cancer Institute).[34,35] Food groups were derived from the United States Department of Agriculture MyPyramid equivalents Database and macro- and micronutrients were derived from United States Department of Agriculture Food and Nutrient Database for Dietary Studies.[36] Healthy Eating Index (HEI) 2010 is an index of diet quality that indicates conformance to 2010 Dietary Guidelines for Americans. Scores are derived from adequacy and moderation variables that include calorie-adjusted food groups and specific nutrients;[37] scores were calculated using SAS, Version 9.4 (SAS Institute, Inc., Cary, NC, USA). Variables and values for all nutrients were analyzed with and without vitamin and mineral supplements. The average intake variables of the two recalls at each time point were used for reporting and analyses. Anthropometrics were obtained using standard procedures,[38] and prostate cancer Gleason sum data on diagnostic biopsies were obtained from the patients' medical records. Gleason sum is a score that pathologists use to classify both the major and minor histological pattern of prostatic tumor, with "1" assigned to tumors that are least aggressive and "5" to tumors that are most aggressive; a Gleason sum adds scores for major and minor patterns together.[39]

Fecal samples were collected after a bowel movement on sterile wipes and stored in sealed plastic bags; participants were instructed to store them in their freezer until the time of their appointment, and were subsequently stored at −80°C until batch analyzed. Microbiome analysis methods were previously reported by Demark-Wahnefried et al.[31] Microbe DNA was extracted using a ZR Fecal DNA Miniprep, and the V4 region of the 16S rRNA gene was PCR-amplified and sequenced using the Illumina Miseq, as previously described.[40, 41] Analyses were performed with the Quantitative Insight into Microbial Ecology (QIIME) suite, version 1.7,[42] and a wrapper for QIIME (i.e., QWRAP).[40] Operational taxonomic units (OTUs) were selected with uclust (a QIIME algorithm to cluster gene sequences) at 97% similarity; which is indicative of most 16S rRNA genes at the genus level. OTUs were aligned with PyNAST (in QIIME), and OTUs with abundance < 0.0005% were filtered.[43] Taxonomic assignments to OTUs were performed with the Ribosomal Database Project classifier,[44] informed by the May 2013 version of the Greengenes 16S database.[45] The final filtered OTU table was used to generate taxonomy charts and to calculate alpha and beta diversity. Within-sample (alpha) diversity measures were calculated using observed species, Shannon Index, and whole tree Phylogenetic Diversity.[29, 46] Beta diversity was calculated using Bray Curtis and weighted and unweighted Unifrac clustering of donors based on their microbial composition.[47] Principal coordinates analysis (PCoA) was performed by QIIME

to visualize the dissimilarity matrix (beta-diversity) among the samples. Samples in PCoA plots were colored based on the grouping variables used in beta diversity analysis.

Statistics

Dietary intake variables were analyzed longitudinally by calculating magnitude of change from baseline to follow-up and dichotomizing the total sample based on median change values. For baseline analyses, absolute intake amounts were dichotomized. Individual nutrients and food groups with significantly different clustering (as visualized on PCoA plots and statistically with beta diversity metrics, PERMANOVA $p<0.05$) between halves of intake change were tested for differences in individual taxa frequencies. Operational Taxonomic Units (OTUs) were grouped by phyla, classes, orders, families, genera and species and tested for significant differences on all taxonomic levels individually in frequency between groups (Kruskal Wallis $p<0.05$ after false discovery rate [FDR] correction). Taxonomic units with significant differences were retained for further analysis of associations between diet and microbiome composition. Median tests were used for post-hoc analyses of dichotomized dietary variables that were found to be significantly associated with changes in OTUs.

Associations between nutritional factors and taxonomic groups were examined at baseline and longitudinally using Spearman correlations on continuous variables. Due to the small sample size and non-normal distribution of microbiome data, medians are reported and tested for between and within arm differences. Baseline anthropometrics, dietary factors, alpha diversity and specific OTUs were compared between study arms using Mann Whitney U-tests. Longitudinal changes in anthropometrics, dietary factors and specific OTUs were analyzed using Wilcoxon Signed Rank tests within study arms. P-values of 0.05 or less were considered statistically significant.

Results

Participant characteristics

Men participating in this substudy were on average 60.9 years old, weighed 98.9 kg, had a BMI of 31.6 kg/m^2, and were on the study 53 days. Sixty-eight percent of participants were non-Hispanic white males (n=15), and 32% (n=7) were non-Hispanic black males. The majority (n=13, 59%) of men had biopsy Gleason sums of seven, while three had scores of eight, and six had a score of six. There were no differences in race or Gleason sum between study arms (Fisher's exact tests $p=1.000$, $p=0.781$ for race and Gleason sum, respectively). Five men in each arm were taking medications known to affect the microbiome throughout the study. In the intervention arm, men took metformin (n=1); proton pump inhibitors (PPIs) (n=2); and non-steroidal anti-inflammatory drugs (NSAIDs) (n=2). In the control arm, men took metformin (n=1); metformin and PPI (n=1); NSAID and PPI (n=2); and NSAID (n=1). Antibiotic use was not reported by any participants while on the study.

Microbiome composition and alpha-diversity

At baseline, alpha diversity did not differ between study arms (Mann-Whitney U-test $p=0.332$, $p=0.401$, $p=0.365$) for observed species, Shannon Index, and whole tree

Phylogenetic Diversity, respectively). Four phyla present in fecal samples represented 1% or more of the microbiome composition. Median proportions of Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria were 0.61, 0.19, 0.06 and 0.02, respectively (Table 1). Additionally, fifteen genera, which represented greater than 0.01% relative abundance in all samples are presented in Table 1. At baseline, no between-arm differences in beta diversity or OTUs were observed; moreover, the most abundant OTUs and Firmicutes to Bacteroidetes (F:B) ratio did not differ within study arms over time.

Gleason sum and microbiota

Correlation coefficients with corresponding p-values for associations between OTUs and Gleason sum are reported in Table 2. Gleason sum was positively associated with the phylum Deferribacteres (p=0.032) and several Proteobacteria taxa including *Caulobacterales* (p=0.048), *Burkholderiales* (p=0.025), and *Pasteurellales* (p=0.028). Gleason sum also was positively associated with *Clostridium* (p=0.005) and inversely associated with *Blautia* (p=0.049), both of the phylum Firmicutes.

Between-arm and baseline correlative analyses

Nutrient and food group intake and body weight status are reported in Table 3. At baseline, there were no between-arm differences in nutrients, food groups or diet quality scores. The weight loss arm reported decreasing total calories, total carbohydrates, and total grains while there were no reported changes in the control arm. Diet quality did not change for either arm, though the weight loss arm did experience significant weight loss. Beta diversity analysis indicated no significant effect of weight loss (Weighted Unifrac FDR p=0.258) or self-reported physical activity (Weighted Unifrac FDR p=0.235) on the composition of fecal microbiota. Beta diversity analyses of nutrients and food groups in the entire sample revealed differences in several taxa, which were further analyzed for associations with dietary factors.

Baseline associations between dietary intake and microbiota indicate that men who consumed more calories did so from all macronutrients and food groups (baseline correlation data not shown). Positive correlations were observed between Bacteroidetes and protein intake. Protein intake was inversely correlated with the F:B ratio and Actinobacteria. *Campylobacterales* (phylum Proteobacteria) was positively associated with fiber and sugar, dark green vegetables and fruit, and Verrucomicrobia (*Akkermansia Muciniphila* represented >99% of this phylum) was positively correlated with orange vegetables at baseline. HEI-2010 scores were inversely associated with *Lactobacillus* (phylum Firmicutes) and positively correlated with *Campylobacterales* and *Verrucomicrobiales* (data not shown).

Beta-diversity and PERMANOVA analyses

Changes in nutrients and food groups resulting in dissimilar microbiota were evaluated by Bray-Curtis, Unweighted Unifrac and Weighted Unifrac clustering analysis (See Supplementary Figure). Clustering by nutrients and food groups with significant differences for all three methods were poultry, meat, and lutein and zeaxanthin. The food groups orange vegetables, eggs, potatoes, milk, and low omega-3 fish; nutrients lycopene, vitamin D, vitamin B12, choline, cholesterol, alcohol, and caffeine; and the fatty acids eicosapentaenoic

acid, paullinic acid, and palmitoleic acid were significantly different for at least one beta diversity metric. Taxa level analyses for each of these variables were conducted and 43 taxa were significantly different, with FDR corrected $p < 0.05$ (see supplementary data). Comparing high and low intakes of eggs at baseline (essentially non-consumers vs. consumers of whole eggs, median 0.378 ounces/day including mixed dishes), 26 OTUs differed between groups. Seventeen of the OTUs were in the phylum Proteobacteria, and were lower for egg consumers than non-consumers. Post-hoc analyses indicated men who increased poultry intake had lower levels of *Clostridiales* than men who had no or negative change in intake (Median test, p=0.009). Correlations between changes in dietary variables and changes in OTUs are shown in Figure 1. *Bacteroides* were positively and *Escherichia* (phylum Proteobacteria) were negatively associated with change in total calories ($p<0.048$, $p<0.001$ for *Bacteroides* and *Escherichia*, respectively), protein (p=0.002, p=0.005), and fat (p=0.023, p=0.001). Change in red meat consumption was inversely associated with several small OTUs including *Flavobacteriales* (phylum Bacteroidetes) (p=0.011), *YS2* (phylum Cyanobacteria) (p=0.009), *Deferribacteres* (p=0.028), *Bacillales* (p=0.027) and *Turicibacterales* (p=0.05) (phylum Firmicutes), *Burkholderiales* (p=0.005), *Pasteurellales* (p=0.033), *Pseudomonadales* (p=0.001) and *Xanthomonadales* (p=0.042) (phylum Proteobacteria), and Tenericutes (p=0.029). Change in choline intake was associated with several OTUs in addition to those related to protein food consumption, notably its inverse correlation to *Lactobacillus* (p=0.024), *Clostridium* (p=0.038) and *Escherichia* (p=0.015).

Discussion

In this first reported study to investigate changes in the microbiota that occur with dietary change in men with prostate cancer, fecal microbes reflected dietary factors and changes expected over the course of the study. Baseline characteristics of the microbiome, namely elevated Proteobacteria levels were fairly unique and were comparable only to previous reports of ileal Crohn's Disease,[48] which was not present in any of our participants. At baseline, *Bacteroides* were elevated compared to *Prevotella*. The relative abundance of *Prevotella* or *Bacteroides* is driven by the presence of high plant fiber vs refined, fat and protein based diets, respectively.[49] Previous work has established three enterotypes based on statistical clustering across multiple geographical regions with differing enrichment of only three genera within two phyla: the *Bacteroides* and *Prevotella* (phylum Bacteroidetes) and *Ruminoccocus* (phylum Firmicutes).[50] It could be hypothesized that diet quality would be reflected in the microbial composition given the abundance of fiber digesting *Prevotella*, among several other species. While increased *Bacteroides* may not be directly associated with disease risk, it is reflective of diet quality. While these prostate cancer patients may have changed their diet from prediagnosis, their diet quality, as measured by the HEI-2010, was comparable to nationally representative adult cancer survivors of the same age.[51]

As reflected in the lack of change in diet quality, men in this study decreased calories from all food sources, rather than replacing energy dense foods with nutrient dense choices. Several genera in the phylum Firmicutes were abundant across all participants. The unexpected correlations with several Firmicutes and Proteobacteria genera and biopsy Gleason sum at diagnosis is noteworthy; a case-control study of hospitalized adults prior to *C. difficile* infection found that individuals who developed the infection had altered levels of

several OTUs,[52] reiterating that dysbiosis allows opportunistic bacteria to increase in abundance. In this sample of men with prostate cancer, we hypothesize that elevated levels of opportunistic Proteobacteria contribute to systemic inflammation which may potentiate disease onset or progression.

It has been observed that obese individuals have greater F:B ratios compared to lean individuals.[8] Similarly, decreases in the F:B ratio have been documented in individuals losing weight,[22] and an increase in F:B ratio can be observed with short-term overfeeding, or positive energy balance.[24] In our study, the F:B ratio did not differ between study arms or over time within study arms. Though our intervention period was brief and although several men lost 5 kilograms or more, their follow-up BMIs were still in the overweight or obese category.

Actinobacteria are gram positive, primarily composed of the beneficial genus *Bifidobacterium*, [21] and have been recognized as the third most abundant phylum in healthy adults.[29] However, Proteobacteria were more abundant in our study participants both before and after the intervention. Increases in Proteobacteria have been characteristic of dysbiosis, often accompanied by a decrease in Bacteroidetes and Actinobacteria. Gram negative bacteria, which comprise the Bacteroidetes and Proteobacteria phyla, contain lipopolysaccharide membranes, but are not constitutively pathogenic.[53] These phyla appear to increase and decrease with over- and underfeeding, respectively, suggesting that their concentrations may be a proxy for energy balance.[24] Proteobacteria are generally elevated in obesity but do not exponentially outnumber Actinobacteria as in this study. An abundance of potentially pathogenic gram negative bacteria is associated with dysbiosis due to translocation of bacteria,[12] their structural proteins,[54] lipopolysaccharide[55] and their metabolic byproducts into the bloodstream. Gram negative bacteria have also been observed in atherosclerotic and periodontic plaque,[56] suggesting that translocation through the gut lining may promote other chronic disease states. Additionally, intestinal permeability through various mechanisms can allow for excessive absorption of nutritive and non-nutritive metabolites, which is often implicated in obesity.[12] Taken together, these findings suggest the potential for a microbiome signature of aggressive prostate cancer. While intriguing, given that this study was performed in a relatively circumscribed geographic area, such findings need to be validated with larger studies from diverse populations. Furthermore, such studies also would warrant the inclusion of healthy controls as well as sufficient numbers of men with either benign variants or precursor lesions (e.g., high grade prostatic intraepithelial neoplasia).

The relationship between nutrient and food group changes and microbe composition suggests larger scale studies are warranted. The decrease in Clostridiales by participants who increased poultry consumption, and decreases in several taxa observed with increased red meat consumption may suggest a microbiome altering effect of those food sources, whether directly or through transfer of antibiotic resistance genes in those foods.[57]

While this is one of the first studies to investigate changes in the microbiota in response to dietary change in men with prostate cancer, and is strengthened by being part of a randomized controlled trial, there are some limitations which should be acknowledged. The

first limitation is that it is a post-hoc analysis and therefore findings should be viewed from the standpoint of hypothesis-generation rather than hypothesis testing. Secondly, our intervention period was brief and may not have allowed sufficient time for some populations of microbiota to shift. Thirdly, this study was conducted in the southeastern United States and the dietary and environmental exposures may be unique to this region; therefore, generalizability cannot be assumed. Other exposures that are known to affect the microbiome, such as metformin, PPIs and NSAIDs, were taken by almost half of the study participants throughout the study. Though this may have affected their microbe composition at both time points, it is unknown whether these medications mediate microbe composition change associated with diet change. Additionally, dietary data were obtained from self-report rather than direct observation. Finally, our sample size is modest and while it rivals many other reported longitudinal studies in this arena, larger studies are needed for validation.

Conclusion

In summary, this longitudinal study utilized beta diversity by differences in food and nutrient consumption to characterize the relationship between diet and microbes. Moreover, our data serve as a starting point and document that overweight and obese men with prostate cancer may be dysbiotic and manifest a unique microbiome profile. Further investigation is warranted to determine if a microbiotic signature of prostate cancer exists, whether it is causative, and if it can be manipulated with diet and exercise to serve in efforts aimed toward cancer prevention and control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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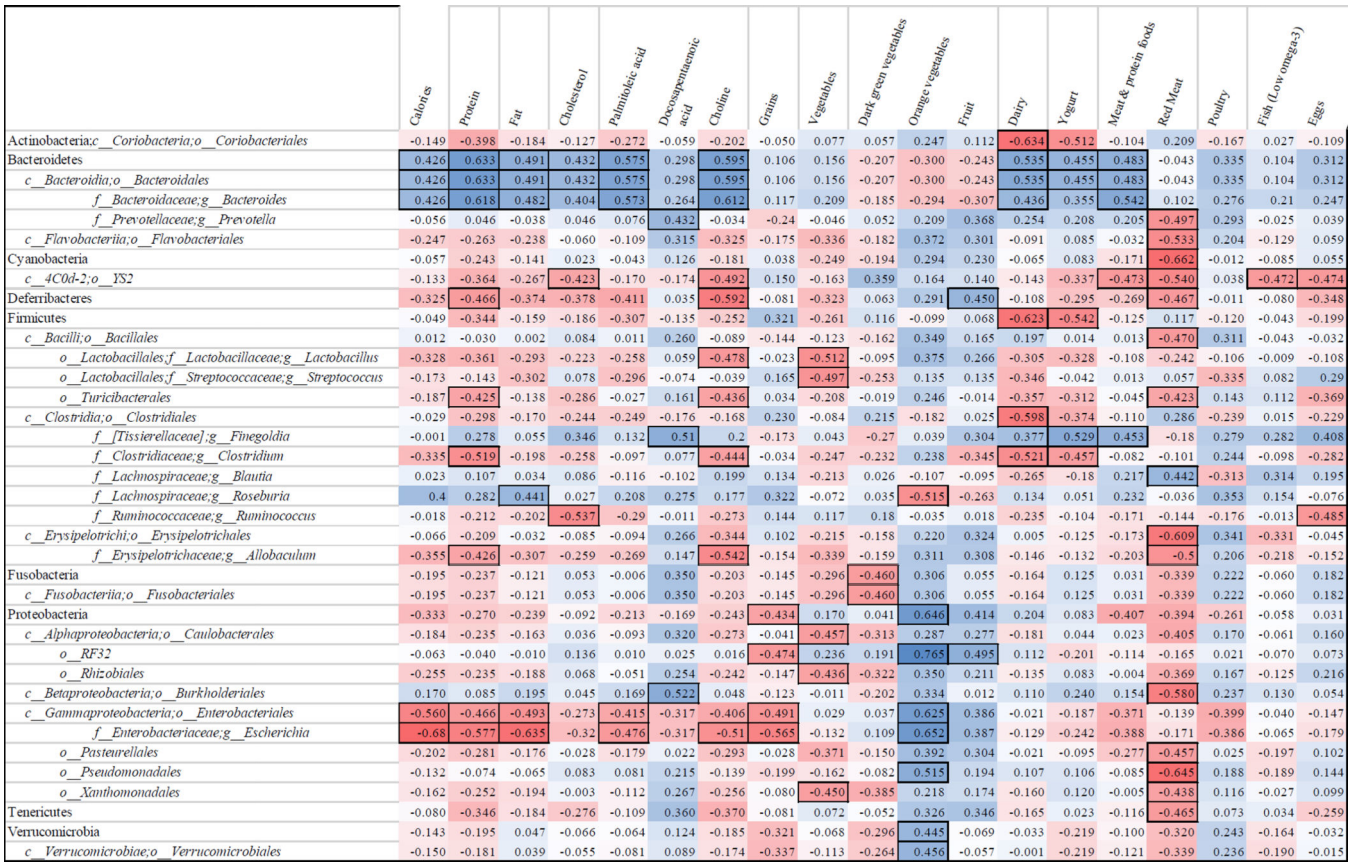

	Calories	Protein	Fat	Cholesterol	Palmitoleic acid	Docosapentaenoic acid	Choline	Grains	Vegetables	Dark green vegetables	Orange vegetables	Fruit	Dairy	Yogurt	Meat & protein foods	Red Meat	Poultry	Fish (Low omega-3)	Eggs
Actinobacteria;c__Coriobacteria;o__Coriobacteriales	-0.149	-0.398	-0.184	-0.127	-0.272	-0.059	-0.202	-0.050	0.077	0.057	0.247	0.112	-0.634	-0.512	-0.104	0.209	-0.167	0.027	-0.109
Bacteroidetes	0.426	0.633	0.491	0.432	0.575	0.298	0.595	0.106	0.156	-0.207	-0.300	-0.243	0.535	0.455	0.483	-0.043	0.335	0.104	0.312
c__Bacteroidia;o__Bacteroidales	0.426	0.633	0.491	0.432	0.575	0.298	0.595	0.106	0.156	-0.207	-0.300	-0.243	0.535	0.455	0.483	-0.043	0.335	0.104	0.312
f__Bacteroidaceae;g__Bacteroides	0.426	0.618	0.482	0.404	0.573	0.264	0.612	0.117	0.209	-0.185	-0.294	-0.307	0.436	0.355	0.542	0.102	0.276	0.21	0.247
f__Prevotellaceae;g__Prevotella	-0.056	0.046	-0.038	0.046	0.076	0.432	-0.034	-0.24	-0.046	0.052	0.209	0.368	0.254	0.208	0.205	-0.497	0.293	-0.025	0.039
c__Flavobacteriia;o__Flavobacteriales	-0.247	-0.263	-0.238	-0.060	-0.109	0.315	-0.325	-0.175	-0.336	-0.182	0.372	0.301	-0.091	0.085	-0.032	-0.533	0.204	-0.129	0.059
Cyanobacteria	-0.057	-0.243	-0.141	0.023	-0.043	0.126	-0.181	0.038	-0.249	-0.194	0.294	0.230	-0.065	0.083	-0.171	-0.662	-0.012	-0.085	0.055
c__4C0d-2;o__YS2	-0.133	-0.364	-0.267	-0.423	-0.170	-0.174	-0.492	0.150	-0.163	0.359	0.164	0.140	-0.143	-0.337	-0.473	-0.540	0.038	-0.472	-0.474
Deferribacteres	-0.325	-0.466	-0.374	-0.378	-0.411	0.035	-0.592	-0.081	-0.323	0.063	0.291	0.450	-0.108	-0.295	-0.269	-0.467	-0.011	-0.080	-0.348
Firmicutes	-0.049	-0.344	-0.159	-0.186	-0.307	-0.135	-0.252	0.321	-0.261	0.116	-0.099	0.068	-0.623	-0.542	-0.125	0.117	-0.120	-0.043	-0.199
c__Bacilli;o__Bacillales	0.012	-0.030	0.002	0.084	0.011	0.260	-0.089	-0.144	-0.123	-0.162	0.349	0.165	0.197	0.014	0.013	-0.470	0.311	-0.043	-0.032
o__Lactobacillales;f__Lactobacillaceae;g__Lactobacillus	-0.328	-0.361	-0.293	-0.223	-0.258	0.059	-0.478	-0.023	-0.512	-0.095	0.375	0.266	-0.305	-0.328	-0.108	-0.242	-0.106	-0.009	-0.108
o__Lactobacillales;f__Streptococcaceae;g__Streptococcus	-0.173	-0.143	-0.302	0.078	-0.296	-0.074	-0.039	0.165	-0.497	-0.253	0.135	0.135	-0.346	-0.042	0.013	0.057	-0.335	0.082	0.29
o__Turicibacterales	-0.187	-0.425	-0.138	-0.286	-0.027	0.161	-0.436	0.034	-0.208	-0.019	0.246	-0.014	-0.357	-0.312	-0.045	-0.423	0.143	0.112	-0.369
c__Clostridia;o__Clostridiales	-0.029	-0.298	-0.170	-0.244	-0.249	-0.176	-0.168	0.230	-0.084	0.215	-0.182	0.025	-0.598	-0.374	-0.110	0.286	-0.239	0.015	-0.229
f__[Tissierellaceae];g__Finegoldia	-0.001	0.278	0.055	0.346	0.132	0.51	0.2	-0.173	0.043	-0.27	0.039	0.304	0.377	0.529	0.453	-0.18	0.279	0.282	0.408
f__Clostridiaceae;g__Clostridium	-0.335	-0.519	-0.198	-0.258	-0.097	0.077	-0.444	-0.034	-0.247	-0.232	0.238	-0.345	-0.521	-0.457	-0.082	-0.101	0.244	-0.098	-0.282
f__Lachnospiraceae;g__Blautia	0.023	0.107	0.034	0.086	-0.116	-0.102	0.199	0.134	-0.213	0.026	-0.107	-0.095	-0.265	-0.18	0.217	0.442	-0.313	0.314	0.195
f__Lachnospiraceae;g__Roseburia	0.4	0.282	0.441	0.027	0.208	0.275	0.177	0.322	-0.072	0.035	-0.515	-0.263	0.134	0.051	0.232	-0.036	0.353	0.154	-0.076
f__Ruminococcaceae;g__Ruminococcus	-0.018	-0.212	-0.202	-0.537	-0.29	-0.011	-0.273	0.144	0.117	0.18	-0.035	0.018	-0.235	-0.104	-0.171	-0.144	-0.176	-0.013	-0.485
c__Erysipelotrichi;o__Erysipelotrichales	-0.066	-0.209	-0.032	-0.085	-0.094	0.266	-0.344	0.102	-0.215	-0.158	0.220	0.324	0.005	-0.125	-0.173	-0.609	0.341	-0.331	-0.045
f__Erysipelotrichaceae;g__Allobaculum	-0.355	-0.426	-0.307	-0.259	-0.269	0.147	-0.542	-0.154	-0.339	-0.159	0.311	0.308	-0.146	-0.132	-0.203	-0.5	0.206	-0.218	-0.152
Fusobacteria	-0.195	-0.237	-0.121	0.053	-0.006	0.350	-0.203	-0.145	-0.296	-0.460	0.306	0.055	-0.164	0.125	0.031	-0.339	0.222	-0.060	0.182
c__Fusobacteriia;o__Fusobacteriales	-0.195	-0.237	-0.121	0.053	-0.006	0.350	-0.203	-0.145	-0.296	-0.460	0.306	0.055	-0.164	0.125	0.031	-0.339	0.222	-0.060	0.182
Proteobacteria	-0.333	-0.270	-0.239	-0.092	-0.213	-0.169	-0.243	-0.434	0.170	0.041	0.646	0.414	0.204	0.083	-0.407	-0.394	-0.261	-0.058	0.031
c__Alphaproteobacteria;o__Caulobacterales	-0.184	-0.235	-0.163	0.036	-0.093	0.320	-0.273	-0.041	-0.457	-0.313	0.287	0.277	-0.181	0.044	0.023	-0.405	0.170	-0.061	0.160
o__RF32	-0.063	-0.040	-0.010	0.136	0.010	0.025	0.016	-0.474	0.236	0.191	0.765	0.495	0.112	-0.201	-0.114	-0.165	0.021	-0.070	0.073
o__Rhizobiales	-0.255	-0.235	-0.188	0.068	-0.051	0.254	-0.242	-0.147	-0.436	-0.322	0.350	0.211	-0.135	0.083	-0.004	-0.369	0.167	-0.125	0.216
c__Betaproteobacteria;o__Burkholderiales	0.170	0.085	0.195	0.045	0.169	0.522	0.048	-0.123	-0.011	-0.202	0.334	0.012	0.110	0.240	0.154	-0.580	0.237	0.130	0.054
c__Gammaproteobacteria;o__Enterobacteriales	-0.560	-0.466	-0.493	-0.273	-0.415	-0.317	-0.406	-0.491	0.029	0.037	0.625	0.386	-0.021	-0.187	-0.371	-0.139	-0.399	-0.040	-0.147
f__Enterobacteriaceae;g__Escherichia	-0.68	-0.577	-0.635	-0.32	-0.476	-0.317	-0.51	-0.565	-0.132	0.109	0.652	0.387	-0.129	-0.242	-0.388	-0.171	-0.386	-0.065	-0.179
o__Pasteurellales	-0.202	-0.281	-0.176	-0.028	-0.179	0.022	-0.293	-0.028	-0.371	-0.150	0.392	0.304	-0.021	-0.095	-0.277	-0.457	0.025	-0.197	0.102
o__Pseudomonadales	-0.132	-0.074	-0.065	0.083	0.081	0.215	-0.139	-0.199	-0.162	-0.082	0.515	0.194	0.107	0.106	-0.085	-0.645	0.188	-0.189	0.144
o__Xanthomonadales	-0.162	-0.252	-0.194	-0.003	-0.112	0.267	-0.256	-0.080	-0.450	-0.385	0.218	0.174	-0.160	0.120	-0.005	-0.438	0.116	-0.027	0.099
Tenericutes	-0.080	-0.346	-0.184	-0.276	-0.109	0.360	-0.370	-0.081	0.072	-0.052	0.326	0.346	-0.165	0.023	-0.116	-0.465	0.073	0.034	-0.259
Verrucomicrobia	-0.143	-0.195	0.047	-0.066	-0.064	0.124	-0.185	-0.321	-0.068	-0.296	0.445	-0.069	-0.033	-0.219	-0.100	-0.320	0.243	-0.164	-0.032
c__Verrucomicrobiae;o__Verrucomicrobiales	-0.150	-0.181	0.039	-0.055	-0.081	0.089	-0.174	-0.337	-0.113	-0.264	0.456	-0.057	-0.001	-0.219	-0.121	-0.339	0.236	-0.190	-0.015

Figure 1.

Spearman's rank correlations between change in nutrient and food groups with change in fecal microbes in 22 men with prostate cancer over the duration of a presurgical weightloss trial. a,b

[a] The first row lists food groups and nutrients that associated with microbe changes in beta diversity tests. The first column lists taxa that changed with changes in nutrient intake. The numbers in the grid are Spearman's rank correlation coefficients. Squares are colored on a red to white to blue scale from negative to positive (−1 to 1). Squares in boxes have p values <0.05. Operational Taxonomic Unit levels are abbreviated as follows: c__ class, o__order, f__family, g__genus.

[b] Two 24 hour dietary recalls were obtained at baseline and at follow-up and entered into National Cancer Institute ASA24 dietary assessment software.

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Table 1

Baseline and follow-up fecal microbe composition[a] of 22 men with prostate cancer over the duration of a presurgical weight loss trial.

	Weight loss group (n=11)					Control group (n=11)					Between Groups
	Baseline		Follow-up		Change[b]	Baseline		Follow-up		Change[b]	Change[c]
	Median	IQR	Median	IQR	p-value	Median	IQR	Median	IQR	p-value	p-value
Actinobacteria	0.0236	0.0115, 0.0880	0.0348	0.0072, 0.0466	0.859	0.0179	0.0115, 0.0313	0.0296	0.0194, 0.0457	0.062	0.270
Corynebacterium	0.0037	0.0003, 0.0116	0.0011	0.0001, 0.0078	0.929	0.0030	0.0007, 0.0227	0.0054	0.0008, 0.0684	0.182	0.898
Bifidobacterium	0.0026	0.0005, 0.0052	0.0018	0.0001, 0.0161	0.374	0.0031	0.0007, 0.0102	0.0092	0.0072, 0.0182	0.110	0.401
Bacteroidetes	0.1845	0.1180, 0.4433	0.2578	0.1770, 0.3510	0.859	0.1911	0.0754, 0.3706	0.1572	0.1272, 0.2604	0.534	0.699
Bacteroides	0.2078	0.0623, 0.3674	0.1603	0.1112, 0.2630	0.213	0.1150	0.0159, 0.1723	0.0636	0.0497, 0.2789	0.374	0.847
Prevotella	0.0059	0.0003, 0.0305	0.0038	0.0002, 0.0325	0.424	0.0142	0.0041, 0.0269	0.0188	0.0025, 0.0439	0.859	0.652
Firmicutes	0.6508	0.5294, 0.7729	0.5899	0.4636, 0.7398	0.424	0.5702	0.3658, 0.7935	0.7164	0.5925, 0.7861	0.110	0.151
Blautia	0.1124	0.0563, 0.2068	0.1678	0.0257, 0.2425	0.534	0.0505	0.0294, 0.0887	0.0586	0.0293, 0.1989	0.477	0.519
Faecalibacterium	0.0703	0.0507, 0.0921	0.0566	0.0381, 0.1296	1.000	0.0669	0.0246, 0.0972	0.0290	0.0079, 0.0660	0.286	0.332
Roseburia	0.0500	0.0178, 0.0879	0.0485	0.0012, 0.0566	0.155	0.0280	0.0123, 0.0575	0.0108	0.0031, 0.0604	0.790	0.847
Ruminococcus	0.0207	0.0056, 0.0439	0.0190	0.0108, 0.0392	0.790	0.0192	0.0111, 0.0535	0.0120	0.0065, 0.0298	0.328	0.478
Clostridium	0.0058	0.0013, 0.0098	0.0056	0.0034, 0.0077	0.929	0.0073	0.0010, 0.0108	0.0054	0.0005, 0.0126	1.000	0.217
SMB53	0.0053	0.0009, 0.0113	0.0060	0.0002, 0.0204	0.424	0.0052	0.0004, 0.0185	0.0044	0.0023, 0.0096	0.929	0.847
Finegoldia	0.0031	0.0006, 0.0088	0.0015	0.0007, 0.0074	0.534	0.0032	0.0005, 0.0105	0.0100	0.0019, 0.0514	0.075	0.974
Streptococcus	0.0030	0.0016, 0.0309	0.0052	0.0022, 0.0589	0.722	0.0061	0.0015, 0.0254	0.0054	0.0027, 0.0178	0.790	0.519
Allobaculum	0.0007	0.0002, 0.0019	0.0013	0.0003, 0.0474	0.374	0.0006	0.0001, 0.0148	0.0008	0.0002, 0.0080	1.000	0.797
Lactobacillus	0.0004	0.0003, 0.0037	0.0009	0.0003, 0.0044	0.859	0.0021	0.0006, 0.0113	0.0028	0.0007, 0.0041	0.424	0.974
Proteobacteria	0.0223	0.0087, 0.0816	0.0328	0.0201, 0.1392	0.657	0.1434	0.0239, 0.1910	0.0513	0.0172, 0.0899	0.131	0.133
Escherichia	0.0004	0.0002, 0.0049	0.0013	0.0003, 0.0050	0.859	0.0043	0.0008, 0.0273	0.0029	0.0004, 0.0078	0.477	0.300
F:B Ratio[d]	1.81	1.20, 5.25	2.81	1.62, 5.29	0.790	4.44	1.88, 17.19	3.78	1.63, 5.67	0.155	0.365

[a] Four major phyla with species representing >0.01% of average composition of all study samples.

[b] Wilcoxon Signed Rank Test was used to determine differences over time within groups.

[c] Mann-Whitney U Test was used to determine difference between groups over time.

^{d}Firmicutes : Bacteroidetes Ratio.

Table 2

Spearman rank correlations between biopsy Gleason sum and baseline operational taxonomic units[a] of fecal microbes in 22 men with prostate cancer.

Operational Taxonomic Unit	ρ	p-value
[Thermi]	0.572	0.005
Bacteroidetes;c__Flavobacteriia;o__Flavobacteriales	0.434	0.044
Deferribacteres	0.458	0.032
Firmicutes;c__Clostridia;o__Clostridiales;f__Clostridiaceae;*g__Clostridium*	0.579	0.005
Firmicutes;c__Clostridia;o__Clostridiales;f__Lachnospiraceae;*g__Blautia*	−0.425	0.049
Proteobacteria;c__Alphaproteobacteria;o__Caulobacterales	0.425	0.048
Proteobacteria;c__Alphaproteobacteria;o__Rhizobiales	0.423	0.05
Proteobacteria;c__Betaproteobacteria;o__Burkholderiales	0.476	0.025
Proteobacteria;c__Gammaproteobacteria;o__Pasteurellales	0.469	0.028

[a]Operational Taxonomic Unit levels are abbreviated as follows: c__ class, o__order, f__family, g__genus

Table 3

Baseline and follow-up weight status and diet[a] composition of 22 men with prostate cancer over the duration of a presurgical weightloss trial.

	Weight loss group (n=11)					Control group (n=11)					Between Groups
	Baseline		Follow-up		Change[c]	Baseline		Follow-up		Change[c]	Change[d]
	Median	IQR	Median	IQR	p	Median	IQR	Median	IQR	p	p
Body Weight (kg)	97.2	89.3, 99.6	88.4	84.5, 96	0.003	100.9	90.8, 110.7	94.6	91.4, 99.7	0.230	0.040
Body Mass Index (kg/m2)	30.2	28.2, 33.5	28.6	26.7, 31.8	0.003	31.3	27.1, 33.5	29.6	27.5, 32.9	0.213	0.056
Total Calories (kcal)	1238	1171, 2251	1151	824, 1308	0.050	1596	977, 1726	1582	1231, 1805	0.859	0.101
Total Protein (g)	58.7	41.8, 71.3	52.2	43.3, 62.2	0.248	72.2	52, 82	63.4	48.5, 90.3	0.929	0.847
Total Fat (g)	60.7	43.6, 82.4	36.4	22.6, 61.7	0.075	85.3	43.2, 92.8	65.5	52.2, 86.6	0.477	0.438
Total Carbohydrate (g)	137.4	83.0, 263.2	88.7	84.1, 153.6	0.041	150.3	99.8, 188.7	153.5	102.1, 220.6	0.477	0.056
Total Sugar (g)	46.9	33.9, 102.1	45.4	28.2, 59.3	0.477	55.5	34.9, 66.2	54.7	36.3, 108.2	0.286	0.270
Total Fiber (g)	13.0	10.9, 22.9	10.0	6.6, 11.9	0.075	11.3	8.9, 14.5	10.0	7.2, 14.0	0.374	0.365
Total Grains (oz. eq.)	4.96	1.42, 5.63	2.84	0.87, 4.07	0.050	3.48	2.76, 5.34	4.67	3.52, 5.47	0.248	0.028
Total Vegetables (cup eq.)	1.45	1.01, 2.08	1.02	0.50, 1.53	0.328	1.74	0.52, 2.45	1.54	0.66, 1.93	0.374	0.748
Total Fruit (cup eq.)	0.45	0.11, 1.48	0.73	0.01, 1.16	0.477	0.51	0.05, 1.47	0.64	0.18, 0.87	0.721	0.438
Total Dairy (cup eq.)	0.46	0.13, 0.88	0.77	0.29, 1.47	0.285	0.90	0.36, 1.56	0.67	0.41, 1.29	0.424	0.193
Total Meat, protein foods (oz. eq.)	3.72	2.69, 5.92	2.43	1.86, 4.53	0.286	4.92	3.83, 6.46	4.36	2.89, 7.02	0.790	0.478
Healthy Eating Index 2010 [b]	64.9	60.8, 72.73	64.0	62.9, 69.6	0.657	65.0	60.22, 68.41	64.7	55.49, 68.31	0.534	0.748

[a] Two 24 hour dietary recalls were obtained at baseline and at follow-up and entered into National Cancer Institute ASA24 dietary assessment software.

[b] The Healthy Eating Index 2010 is a diet quality assessment tool that measures conformance to 2010 Dietary Guidelines for Americans.

[c] Wilcoxin Signed Rank Test was used to determine differences over time within groups.

[d] Mann-Whitney U Test was used to determine difference between groups over time.