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Pre-Diagnostic Carbohydrate Intake and Treatment Failure After Radical Prostatectomy for Early-Stage Prostate Cancer

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Abstract

Purpose: An association between dietary carbohydrate intake and prostate cancer (PCa) prognosis is biologically plausible, but data are scarce. This prospective cohort study examined the relation between pre-diagnostic carbohydrate intake and treatment failure following radical prostatectomy for clinically early-stage PCa.

Methods: We identified 205 men awaiting radical prostatectomy and assessed their usual dietary intake of carbohydrates using the 110-item Block food frequency questionnaire. We also evaluated carbohydrate intake quality using a score based on the consumption of sugars relative to fiber, fat, and protein. Logistic regression analyzed their associations with the odds of treatment failure, defined as a detectable and rising serum prostate-specific antigen (PSA) or receiving androgen deprivation therapy (ADT) within 2 years.

Results: Sucrose consumption was associated with a higher odds and fiber consumption with a lower odds of ADT after accounting for age, race/ethnicity, body mass index, and tumor characteristics (odds ratio [OR] (95% confidence interval [CI]) = 5.68 (1.71, 18.9) for 3rd vs. 1st

sucrose tertile and 0.88 (0.81, 0.96) per gram of fiber/day, respectively). Increasing carbohydrate intake quality also associated with a lower odds of ADT (OR (95%CI) = 0.78 (0.66, 0.92) per unit increase in score, range = 0 to 12).

Conclusions: Pre-diagnostic dietary carbohydrate intake composition and quality influence the risk of primary treatment failure for early-stage PCa. Future studies incorporating molecular aspects of carbohydrate metabolism could clarify possible underlying mechanisms.

Keywords

prostate cancer prognosis; treatment failure; dietary carbohydrate; insulin sensitivity

Background

Prostate cancer (PCa) is one of the most common cancers in the United States (1, 2). The five-year survival rate of prostate cancer (PCa) is high (97.3%) (3), however, in patients presenting with metastatic prostate cancer, the 5-year survival rate declines to 29%, resulting in prostate cancer being the third leading cause of cancer-related deaths in the US (1). Between 20 and 40% of patients who undergo radical prostatectomy for clinically early-stage – and thus potentially curable – prostate cancer eventually fail treatment as indicated by biochemical evidence of persistent or progressive disease (4, 5). Therefore, understanding the modifiable risk factors for primary treatment failure is important for optimizing prostate cancer control and limiting morbidity and mortality from the disease.

Insulin resistance and impaired glucose metabolism are thought to influence PCa recurrence. For instance, elevated glucose levels at PCa diagnosis has been identified as an independent predictor of PCa recurrence (6) and higher concentrations of insulin growth factor-1 (IGF-1) and insulin axis proteins have been linked with poorer prognosis of PCa (7, 8). One potential diet-related risk factor specific to PCa and glucose metabolism is carbohydrate intake. Carbohydrates are of interest because of the influence it is known to exert on glucose and insulin concentrations after consumption. Regarding PCa associated with carbohydrate intake, much of what we know are based on epidemiological studies examining carbohydrate intake and PCa incidence. A recent case-control study has demonstrated the negative associations between carbohydrate intake and the risk of PCa (9). According to a recent meta-analysis (i.e. 13 case control and 6 cohort), there was no increased risk in prostate cancer between those in the highest vs lowest groups of carbohydrate intake (summary RR: 1.06, 95% CI: 0.93–1.20) and similar results were observed by type of study design (i.e. case control, cohort). It has also been proposed that PCa risk differs depending on the type of carbohydrate consumed. While the Health Professionals follow up study found a positive association between intake of whole grains and PCa incidence;(10) pooled estimates from a later meta-analyses of 27 observational studies (18 case controls and 9 cohort studies) found no significant relationships between whole grains, dietary fiber, total carbohydrates, respectively, with incidence of PCa (11). An early prospective study by Giovannucci et al. demonstrated that fruit consumption and higher fructose intake were associated with lower risk of PCa (12). It is important to note that what is known to date examines the relationship between carbohydrate intake and the development of PCa, but much less is known about carbohydrates and PCa recurrence/progression after primary therapy. Studies exploring the

associations between dietary carbohydrate and treatment outcomes for PCa are limited and only preclinical results have been published up to date, such as carbohydrate restriction in mice (13, 14). No human studies were published in association with restricted carbohydrate consumption and PCa outcomes, however, reduced carbohydrate might be related to decreased risk of PCa and its progression in human through weight loss and slow tumor growth (15). Given that impaired glucose metabolism may also play a role in PCa recurrence/progression, the relationship between dietary carbohydrate and primary treatment outcomes is worth exploring further.

The purpose of this study was to examine the relation between usual dietary intake of carbohydrates before diagnosis and treatment failure following radical prostatectomy for clinically early-stage PCa. We hypothesized that carbohydrate intake associates with risk of treatment failure, but the direction of the association would vary depending on the type (or quality) of the carbohydrate. For example, pre-diagnostic intake of simple sugars would positively associate with treatment failure, whereas fiber would be protective.

Materials and Methods

Study Design and Subjects

The source of patients for this analysis was an ongoing prospective cohort study of the body weight status and health outcomes of men diagnosed with clinically localized PCa. The sampling frame consisted of 538 men screened for prostate cancer and diagnosed with clinically localized PCa and waiting for radical prostatectomy between July 2009 and January 2013 at four medical centers (Loyola University Medical Center, Maywood, IL; University of Illinois Hospital & Health Sciences System, Chicago, IL; Edward Hines, Jr. VA Hospital, Hines, IL; John H. Stroger, Jr. Hospital of Cook County, Chicago, IL). After obtaining institutional review board approval at each site, 530 men who were eligible on initial medical record review were contacted, and 223 men were enrolled (42.1%). Of these, 205 men had sufficiently completed data for this analysis.

Assessment of dietary carbohydrate intake

Usual dietary intake was assessed approximately 1 week before surgery using the Block 110-item semi-quantitative food frequency questionnaire (FFQ) administered via interview with a trained research technician. The Block FFQ is widely used in epidemiologic research, since the questionnaire was derived from nationally representative sample for US population, reflecting both portion size and nutrient intake (16, 17). Participants were asked to report their dietary patterns during the 12 months prior to the biopsy diagnosis of the prostate cancer. The frequency and portion of food items were asked, and pictures of portion sizes from ¼ cup to 2 cups were provided to help participants estimate serving sizes. The carbohydrate-related components assessed included digestible carbohydrates (e.g., glucose, fructose, sucrose, total sugars), fiber, and alcohol.

Carbohydrate intake quality

Carbohydrate intake quality was evaluated using the FFQ-reported average daily glycemic index and glycemic load and carbohydrate intake scores based on the average daily

consumption of sugars relative to fiber, fat, and protein. Details on how the scores were constructed are shown in Table 1. We hypothesized that reduced consumption of simple sugars and increased consumption of fiber before diagnosis would associate with a lower risk of primary treatment failure. Therefore, we created two scores, a) a low sugar/high fiber score based on average daily consumption of glucose, fructose, sucrose, and total fiber in grams and b) a low sugar/high fiber score combined with a low fat/high protein score, with the latter based on average daily consumption of fat and protein as percentages of total calories. Intakes were ranked according to tertiles and points assigned. Tertiles for glucose, fructose, and sucrose were based on energy-adjusted residuals of the natural log-transformed nutrient intakes, and those for fiber were based on energy-adjusted residuals of the crude intake (17). *Points* - For sugars and fats, intakes in the first, second, and third tertiles were assigned 2, 1, and 0 points, respectively. Whereas for fiber and protein, intakes in the first, second, and third tertiles were assigned 0, 1, and 2 points, respectively. The carbohydrate intake quality scores were calculating by summing the points assigned as follows:

$$\text{Low sugar/high fiber score} = \text{Glucose}_t(n) + \text{Fructose}_t(n) + \text{Sucrose}_t(n) + \text{Fiber}_t(n) \text{ (range, 0 to 8)}$$

$$\text{Low sugar/high fiber-Low fat/high protein score} = [\text{Low sugar/high fiber score}] + \text{Fat}_t(n) + \text{Protein}_t(n) \text{ (range, 0 to 12)}$$

where t = tertile rank and n = points assigned.

As a result, lower intakes of sugars and fat and higher intakes of fiber and protein would be associated with higher (i.e., better) scores.

Demographic and clinical characteristics

Before surgery, a trained research technician collected demographic information (date of birth, self-reported race/ethnicity, marital status, etc.) using a structured questionnaire and obtained anthropometric measurements (height [cm], weight [kg], and waist and hip circumference [cm]). Pathologic tumor characteristics, including surgical margin status, were determined by central pathology review conducted by a single pathologist (V.M.). Tumors were staged according to the eighth edition of the American Joint Commission on Cancer (AJCC) tumor-node-metastasis (TNM) staging for prostate cancer (2017) then grouped into their corresponding AJCC prognostic stage categories based on TNM stage, prostate-specific antigen (PSA) at diagnosis, and Gleason grade group (18). Seven of the nine AJCC prognostic categories were represented in our sample: I, IIA, IIB, IIC, IIIA, IIIB, and IIIC. The categories were further collapsed to create a three-level “prognostic group” variable for this analysis: Group 1 = I (low recurrence risk), Group 2 = IIA, IIB, or IIC (intermediate recurrence risk), and Group 3 = IIIA, IIIB, and IIIC (high recurrence risk). A positive surgical margin was defined as the presence of cancer cells at the inked margin (19).

Outcome Ascertainment

Serum PSA concentrations were monitored post-operatively every 3 months for the first year, every 3–6 months the second year, and annually thereafter. Alterations to the follow-up protocol were allowed, at the discretion of the treating clinician. Serum PSA measurements were performed using Tandem PSA monoclonal antibody assay (Hybritech, San Diego,

CA). Treatment failure was defined as a detectable (> 0.1 ng/mL) and rising serum prostate-specific antigen (PSA) or receipt of androgen deprivation therapy (ADT) within 2 years after the radical prostatectomy.

Statistical analyses

To compare distributions of demographic, clinical, and diet characteristics between men who experienced treatment failure within 2 years and those who did not, we used chi-square tests for categorized variables and Student's t-tests for continuous variables, and Wald p-values were used to determine statistical significance ($p < 0.05$). Multivariable logistic regression models evaluated the association between pre-diagnostic carbohydrate intake and treatment failure. We focused on energy-adjusted residual intakes of glucose, fructose, sucrose, total sugars, total carbohydrates, and total fiber analyzed either as continuous variables or tertiles. Glucose index and glucose load were analyzed as tertiles, and carbohydrate quality scores were analyzed as continuous variables. Treatment failure was analyzed in two forms: a) "a detectable (> 0.1 ng/mL) and rising PSA or ADT within 2 years" and b) as "ADT within 2 years" only. All models included age at cancer diagnosis, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, and other), study site, body mass index (BMI) (mg/kg^2), prognostic group (3 categories), surgical margin status (positive, yes vs. no), total energy intake (kcal), and percent calories from alcohol as covariates. Finally, we used multivariable logistic regression models to explore the association of treatment failure with consumption of selected carbohydrate-containing foods (fruits, vegetables, whole grains, and sweets) after accounting for age, race/ethnicity, study site, BMI, prognostic group, surgical margin status, and total energy intake. All statistical analyses were performed by SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Demographic, clinical, and dietary characteristics of study participants are summarized in Table 2. Overall, participants were predominantly middle-aged, non-Hispanic white, and tended to present with low-to-intermediate recurrence risk tumors. With regard to dietary carbohydrates, average daily consumption of glucose and fructose was significantly higher by approximately 30% among men who failed treatment within the first two years than among those who did not (30.3 vs. 23.2 grams/day, $p = 0.01$ and 33.6 vs. 25.8 grams/day, $p = 0.02$, respectively). Men who failed treatment also consumed on average nearly 50% more sugary beverages each day (428.7 vs. 289.6 grams, $p = 0.02$) and fewer servings of whole grains (0.6 vs. 0.9 servings/day, $p = 0.06$).

Table 3 presents the association of carbohydrate intake before diagnosis with odds of treatment failure after accounting for participant and tumor characteristics. Sucrose consumption associated with an increased odds of receiving ADT within two years after surgery independent of established clinical predictors (prognostic group, surgical margin status, BMI), demographics (age, race/ethnicity), alcohol and total energy intake (odds ratio [OR] 95% confidence interval [CI] = 5.68 [1.71, 18.9] for highest vs. lowest tertile, OR trend [95% CI] = 2.36 [1.31, 4.26], $p = 0.0045$). In contrast, fiber consumption independently associated with a lower odds of treatment failure within 2 years analyzed either as the

composite endpoint (OR [95% CI] = 0.92 [0.85, 0.99] per gram/day, $p = 0.0416$) or restricted to receipt of ADT (OR [95% CI] = 0.88 [0.81, 0.96] per gram/day, $p = 0.0048$). Fructose and total sugar consumption also associated with an increased odds of receiving ADT, but not in a dose-response manner.

Measures of carbohydrate intake quality also independently associated with treatment failure (Table 4). The odds of receiving ADT within 2 years after surgery was associated with average daily glycemic index (OR [95% CI] = 3.63 [1.05, 12.5] for highest vs. lowest tertile, OR trend [95% CI] = 1.91 [1.03, 3.55], $p = 0.041$). A borderline association with increasing average daily glycemic load was also observed. (OR [95% CI] = 4.52 [0.97, 21.1] for highest vs. lowest tertile, OR trend = 2.12 [0.98, 4.56], $p = 0.055$). However, increasing carbohydrate intake quality scores were independently associated with a lower odds of treatment failure. For example, in the case of the quality score based on the relative consumption of sugar, fiber, fat, and protein (“low sugar/high fiber-low fat/high protein”), the odds of treatment failure decreased as the score increased (OR [95% CI] = 0.75 [0.60, 0.93] per unit increase, $p = 0.022$ for detectable and rising PSA or ADT after surgery, and OR [95% CI] = 0.78 [0.66, 0.92] per unit increase, $p = 0.0036$ for ADT after surgery only).

Finally, Table 5 shows the association between treatment failure with pre-diagnostic consumption of selected carbohydrate-containing foods after accounting for participant and tumor characteristics. Whole grain consumption associated with a lower odds (for detectable and rising PSA or ADT after surgery, OR [95%CI] = 0.30 [0.10, 0.94] for highest vs. lowest tertile, OR trend [95% CI] = 0.54 [0.33 0.98], $p=0.042$). Whereas consumption of dessert sweets increased the odds of treatment failure (for detectable and rising PSA or ADT after surgery, OR [95%CI] = 3.58 [1.19, 10.8] for highest vs. lowest tertile, OR trend = 1.94 [1.11, 3.39], $p = 0.020$, and for ADT after surgery only, OR [95%CI] = 3.47 [1.16, 10.4] for highest vs. lowest tertile, OR trend = 1.89 [1.09, 3.29], $p=0.023$). Consumption of sugary beverages also associate with an increased odds (OR [95%CI] = 3.61 [1.05, 12.4] for highest vs. lowest tertile, OR trend = 1.65 [0.92, 2.98], $p= 0.095$ for ADT only).

Discussion

In our study, the level and quality of dietary carbohydrate intake prior to a diagnosis of clinically organ-confined prostate cancer associated with the risk of treatment after radical prostatectomy independent of established clinical predictors. Consumption of simple sugars such as sucrose associated with an increased risk, whereas fiber consumption and higher carbohydrate intake quality were protective. To our knowledge, there is no published research which elucidates the relationship between surgical treatment outcomes in prostate cancer and dietary carbohydrate intake prior to diagnosis. However, a few studies with mice demonstrated effects of no-carbohydrate ketogenic diet and reduced tumor growth (13, 20), which were inconsistent with the results from this study. The discrepancy may due to the different aspects of carbohydrate components; as our results showed, not every carbohydrate component has negative effects on PCa treatment failure, and we even found protective effect of carbohydrate in whole grains or fibers. The results from our study elucidating the importance of the source of carbohydrate were also supported by results from a recent prospective cohort study. In Seidelmann *et al.*, dietary carbohydrate intake was assessed in

association with all-cause mortality and both low and high quantiles of carbohydrate intake patterns were related with higher mortality, with varying risk by the source of food (21). Further study such as clinical trials would be needed to further elucidate the true associations between carbohydrate intake patterns and clinical outcomes of men diagnosis with clinically early-stage Pca.

Our findings also suggest protective effects of higher intake whole grains on decreased risk of primary treatment failure. Results from epidemiologic studies on whole grains intake and PCa progression are controversial; a meta-analysis including 14 case-control studies presented a negative association (22), whereas more recent cohort studies showed null associations between whole grains and PCa incidence (10, 23–25). The discrepancy may be due, in part, to the different study designs (case control vs cohort) and that the cohort studies examined PCa incidence rather than outcomes related to prognosis. One study showed an inverse association between high fiber diet and risk of aggressive PCa, which supports our results (26).

In our results, foods associated with refined carbohydrate (sugary sweetened beverages and dessert sweets) were also associated with increased risk of treatment failure. There have been only few studies focused on refined carbohydrate, however, the results are consistent with the results from the current study. For example, a preclinical study showed results of associations between high consumption of refined carbohydrate and increased tumor growth, with activation of signaling pathways distal to the insulin receptor in a PCa murine model (14). Therefore, refined carbohydrate consumption could increase the pace of tumor expansion and micro-metastatic potential of prostate cancer before clinical detection, thus increasing the likelihood that aggressive primary therapy will fail to cure or control the disease.

Insulin sensitivity/resistance could underlie an association between carbohydrate intake and primary treatment failure for prostate cancer. Insulin resistance prompts increased insulin production and stimulates the production of insulin-like growth factor 1 (IGF1) but suppresses activities of insulin-like growth factor binding proteins (IGFBP) (27, 28). Those IGF-1 and IGFBP families have been considered to play an important role in incidence of hormonal cancers including PCa (29–31). Positive relationships between serum insulin level and prostate cancer recurrence has also been reported previously (32). Lower levels of circulating IGF-1 is known to be associated with reduced PCa tumor cell growth, while higher level of insulin and IGFBP-1 and -2 are related to increased PCa cell proliferation. Experimental studies have shown the associations between refined carbohydrate intake and hyperinsulinemia (33). Epidemiologic studies also support the positive association between high refined carbohydrate diet and insulin resistance (34–36). On the other hand, higher intake of whole grains and fiber have shown associations with improved insulin sensitivity in previous studies (37–40).

The strengths of this study include standardized ascertainment of outcomes and measurement of BMI, pathologic tumor characteristics, and other covariates across study sites. Also, we related treatment failure not only to individual carbohydrate components of the diet but to the quality of carbohydrate intake as well. Moreover, one of the measures of

quality that we constructed that significantly associated with treatment failure incorporated the relative intakes of fat and protein. Finally, conducting the study in a cohort of men with screening-detected and clinically localized Pca reduced the likelihood that their dietary intake before diagnosis was altered by their disease status.

Measuring the effects of nutrients on Pca risk and prognosis is challenging due to the complex nutrient composition of foods in the diet and the relatively indolent nature of both latent and clinically-detectable tumors (15, 41). Consequently, characterizing pre-diagnostic dietary carbohydrate exposures on the basis of a single food frequency questionnaire is a limitation of this study.

In conclusion, pre-diagnostic carbohydrate may lower or increase the risk of primary treatment failure for early-stage PCa depending on the carbohydrate composition of the diet and quality of the carbohydrate intake. Future studies incorporating molecular aspects of carbohydrate metabolism could clarify possible mechanisms. Taken together, these data could lend additional support for the role of lifestyle in clinical prostate cancer prevention and control.

References

1. American Cancer Society. (2017) Cancer Facts & Figures. Atlanta: American Cancer Society.
2. Siegel RL, Miller KD, Jemal A. (2018) Cancer statistics, 2018. *CA Cancer J Clin.* 68: 7–30. [PubMed: 29313949]
3. Group. USCSW. (2018) Cancer Statistics Data Visualizations Tool, based on November 2017 submission data (1999–2015). U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute.
4. Kolodziej M (2014) Management of biochemically recurrent prostate cancer following local therapy. *Am J Manag Care.* 20: S273–81. [PubMed: 25734963]
5. Paller CJ, Antonarakis ES, Eisenberger MA, Carducci MA. (2013) Management of patients with biochemical recurrence after local therapy for prostate cancer. *Hematol Oncol Clin North Am.* 27: 1205–19, viii. [PubMed: 24188259]
6. Wright JL, Plymate SR, Porter MP, et al. (2013) Hyperglycemia and prostate cancer recurrence in men treated for localized prostate cancer. *Prostate Cancer Prostatic Dis.* 16: 204–8. [PubMed: 23459096]
7. Braga-Basaria M, Dobs AS, Muller DC, et al. (2006) Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 24: 3979–83. [PubMed: 16921050]
8. Ngo TH, Barnard RJ, Leung PS, Cohen P, Aronson WJ. (2003) Insulin-like growth factor I (IGF-I) and IGF binding protein-1 modulate prostate cancer cell growth and apoptosis: possible mediators for the effects of diet and exercise on cancer cell survival. *Endocrinology.* 144: 2319–24. [PubMed: 12746292]
9. Vidal AC, Williams CD, Allott EH, et al. (2015) Carbohydrate intake, glycemic index and prostate cancer risk. *Prostate.* 75: 430–9. [PubMed: 25417840]
10. Nimptsch K, Kenfield S, Jensen MK, et al. (2011) Dietary glycemic index, glycemic load, insulin index, fiber and whole-grain intake in relation to risk of prostate cancer. *Cancer causes & control : CCC* 22: 51–61.
11. Wang RJ, Tang JE, Chen Y, Gao JG. (2015) Dietary fiber, whole grains, carbohydrate, glycemic index, and glycemic load in relation to risk of prostate cancer. *Onco Targets Ther.* 8: 2415–26. [PubMed: 26366096]
12. Giovannucci E, Rimm EB, Wolk A, et al. (1998) Calcium and fructose intake in relation to risk of prostate cancer. *Cancer research.* 58: 442–7. [PubMed: 9458087]

13. Mavropoulos JC, Buschemeyer WC, 3rd, Tewari AK, et al. (2009) The effects of varying dietary carbohydrate and fat content on survival in a murine LNCaP prostate cancer xenograft model. *Cancer Prev Res (Phila)*. 2: 557–65. [PubMed: 19470786]
14. Venkateswaran V, Haddad AQ, Fleshner NE, et al. (2007) Association of diet-induced hyperinsulinemia with accelerated growth of prostate cancer (LNCaP) xenografts. *Journal of the National Cancer Institute*. 99: 1793–800. [PubMed: 18042933]
15. Masko EM, Allott EH, Freedland SJ. (2013) The relationship between nutrition and prostate cancer: is more always better? *Eur Urol*. 63: 810–20. [PubMed: 23219353]
16. Block G, Hartman AM, Dresser CM, Carroll MD, Gannon J, Gardner L. (1986) A databased approach to diet questionnaire design and testing. *American journal of epidemiology*. 124: 453–69. [PubMed: 3740045]
17. Willett W, Stampfer MJ. (1986) Total energy intake: implications for epidemiologic analyses. *American journal of epidemiology*. 124: 17–27. [PubMed: 3521261]
18. Buyyounouski MK, Choyke PL, McKenney JK, et al. (2017) Prostate cancer - major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 67: 245–53. [PubMed: 28222223]
19. Tan PH, Cheng L, Srigley JR, et al. (2011) International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 5: surgical margins. *Mod Pathol*. 24: 48–57. [PubMed: 20729812]
20. Freedland SJ, Mavropoulos J, Wang A, et al. (2008) Carbohydrate restriction, prostate cancer growth, and the insulin-like growth factor axis. *Prostate*. 68: 11–9. [PubMed: 17999389]
21. Seidemann SB, Claggett B, Cheng S, et al. (2018) Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *Lancet Public Health*. 3: e419–e28. [PubMed: 30122560]
22. Jacobs DR, Jr., Marquart L, Slavin J, Kushi LH. (1998) Whole-grain intake and cancer: an expanded review and meta-analysis. *Nutr Cancer*. 30: 85–96. [PubMed: 9589426]
23. Drake I, Sonestedt E, Gullberg B, et al. (2012) Dietary intakes of carbohydrates in relation to prostate cancer risk: a prospective study in the Malmo Diet and Cancer cohort. *The American journal of clinical nutrition*. 96: 1409–18. [PubMed: 23134882]
24. Egeberg R, Olsen A, Christensen J, et al. (2011) Intake of whole-grain products and risk of prostate cancer among men in the Danish Diet, Cancer and Health cohort study. *Cancer causes & control* : CCC. 22: 1133–9. [PubMed: 21656162]
25. Suzuki R, Allen NE, Key TJ, et al. (2009) A prospective analysis of the association between dietary fiber intake and prostate cancer risk in EPIC. *International journal of cancer. Journal international du cancer*. 124: 245–9. [PubMed: 18814263]
26. Tabung F, Steck SE, Su LJ, et al. (2012) Intake of grains and dietary fiber and prostate cancer aggressiveness by race. *Prostate Cancer*. 2012: 323296. [PubMed: 23213538]
27. Mohamed-Ali V, Pinkney JH, Panahloo A, Cwyfan-Hughes S, Holly JM, Yudkin JS. (1999) Insulin-like growth factor binding protein-1 in NIDDM: relationship with the insulin resistance syndrome. *Clin Endocrinol (Oxf)*. 50: 221–8. [PubMed: 10396366]
28. Bang P, Nygren J, Carlsson-Skwirut C, Thorell A, Ljungqvist O. (1998) Postoperative induction of insulin-like growth factor binding protein-3 proteolytic activity: relation to insulin and insulin sensitivity. *J Clin Endocrinol Metab*. 83: 2509–15. [PubMed: 9661636]
29. Hsing AW, Chua S, Jr., Gao YT, et al. (2001) Prostate cancer risk and serum levels of insulin and leptin: a population-based study. *Journal of the National Cancer Institute*. 93: 783–9. [PubMed: 11353789]
30. Wolk A, Mantzoros CS, Andersson SO, et al. (1998) Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. *Journal of the National Cancer Institute*. 90: 911–5. [PubMed: 9637140]
31. Yu H, Rohan T. (2000) Role of the insulin-like growth factor family in cancer development and progression. *Journal of the National Cancer Institute*. 92: 1472–89. [PubMed: 10995803]
32. Lehrer S, Diamond EJ, Stagger S, Stone NN, Stock RG. (2002) Increased serum insulin associated with increased risk of prostate cancer recurrence. *Prostate*. 50: 1–3. [PubMed: 11757030]

33. Voznesenskaya A, Tordoff MG. (2015) Low-calcium diet prevents fructose-induced hyperinsulinemia and ameliorates the response to glucose load in rats. *Nutr Metab (Lond)*. 12: 38. [PubMed: 26516336]
34. Kim Y, Keogh JB, Clifton PM. (2017) Consumption of red and processed meat and refined grains for 4weeks decreases insulin sensitivity in insulin-resistant adults: A randomized crossover study. *Metabolism*. 68: 173–83. [PubMed: 28183449]
35. Lopez-Alarcon M, Perichart-Perera O, Flores-Huerta S, et al. (2014) Excessive refined carbohydrates and scarce micronutrients intakes increase inflammatory mediators and insulin resistance in prepubertal and pubertal obese children independently of obesity. *Mediators Inflamm*. 2014: 849031. [PubMed: 25477716]
36. Zuniga YL, Rebello SA, Oi PL, et al. (2014) Rice and noodle consumption is associated with insulin resistance and hyperglycaemia in an Asian population. *Br J Nutr*. 111: 1118–28. [PubMed: 24229726]
37. Cook LT, O'Reilly GA, Goran MI, Weigensberg MJ, Spruijt-Metz D, Davis JN. (2014) Vegetable consumption is linked to decreased visceral and liver fat and improved insulin resistance in overweight Latino youth. *J Acad Nutr Diet*. 114: 1776–83. [PubMed: 24685236]
38. Damsgaard CT, Biloft-Jensen A, Tetens I, et al. (2017) Whole-Grain Intake, Reflected by Dietary Records and Biomarkers, Is Inversely Associated with Circulating Insulin and Other Cardiometabolic Markers in 8- to 11-Year-Old Children. *The Journal of nutrition*. 147: 816–24. [PubMed: 28356426]
39. Magnúsdóttir OK, Landberg R, Gunnarsdóttir I, et al. (2014) Plasma alkylresorcinols C17:0/C21:0 ratio, a biomarker of relative whole-grain rye intake, is associated to insulin sensitivity: a randomized study. *European journal of clinical nutrition*. 68: 453–8. [PubMed: 24549027]
40. Zhou AL, Hergert N, Rompato G, Lefevre M. (2015) Whole grain oats improve insulin sensitivity and plasma cholesterol profile and modify gut microbiota composition in C57BL/6J mice. *The Journal of nutrition*. 145: 222–30. [PubMed: 25644341]
41. Freedland SJ, Aronson WJ. (2009) Dietary intervention strategies to modulate prostate cancer risk and prognosis. *Curr Opin Urol*. 19: 263–7. [PubMed: 19300265]

Table 1.

Construction of carbohydrate intake scores

	Points		
	0	1	2
<i>Low sugar/high fiber score (range, 0 to 8)^a</i>			
Glucose, grams/day	T3	T2	T1
Fructose, grams/day	T3	T2	T1
Sucrose, grams/day	T3	T2	T1
Fiber, grams/day	T1	T2	T3
<i>Low sugar/high fiber+low fat/high protein score (range, 0 to 12)^b</i>			
Glucose, grams/day	T3	T2	T1
Fructose, grams/day	T3	T2	T1
Sucrose, grams/day	T3	T2	T1
Fiber, grams/day	T1	T2	T3
Percent total fat	T3	T2	T1
Percent total protein	T1	T2	T3

Note: T, tertile.

^aGlucose, fructose, and sucrose tertiles are based on the energy-adjusted residuals of the log-transformed nutrient intakes, whereas fiber tertiles are based on the energy-adjusted residuals of the crude intake

^b“Low sugar/high fiber score” plus sum of the tertile ranks of total fat and total protein intake as a percentage of total calories. Lower intakes of sugars and fat and higher intakes of fiber and protein are associated with higher (i.e., better) scores.

Table 2.**Demographic, Clinical, and Dietary Characteristics of Participants**

		Treatment Failure ^a		
Characteristic	Overall (n=205)	Yes (n=52)	No (n=153)	P
Demographic				
Age at diagnosis, N (%)				
45 to 64 years	156 (76.1)	44 (84.6)	112 (73.2)	0.1
65 years or older	49 (23.9)	8 (15.4)	41 (26.8)	
Race/ethnicity, N (%)				
Black, Non-Hispanic	56 (27.3)	13 (25.0)	43 (28.1)	0.61
White, Non-Hispanic	126 (61.5)	31 (59.6)	95 (62.1)	
Hispanic	19 (9.3)	6 (11.5)	13 (8.5)	
Other	4 (1.9)	2 (3.9)	2 (1.3)	
Clinical				
Prognostic group ^b , N (%)				
Group 1 (low recurrence risk)	66 (32.2)	7 (13.5)	59 (38.6)	<0.001
Group 2 (intermediate recurrence risk)	94 (45.8)	15 (28.9)	79 (51.6)	
Group 3 (high recurrence risk)	44 (22.0)	30 (57.7)	15 (9.8)	
Tumor-positive surgical margin, N (%)	73 (35.6)	34 (64.7)	39 (25.5)	<0.001
Body mass index, kg/m ²	28.8 (4.2)	29.5 (4.2)	28.5 (4.2)	0.16
Daily dietary intake, mean (SD)				
Total energy (kcal)	2008 (967)	2142 (899)	1963 (990)	0.25
Total carbohydrate (grams)	231.3 (110.1)	249.2 (103.8)	225.2 (111.9)	0.17
Total fat (grams)	82.3 (44.3)	87.1 (43.8)	80.7 (44.5)	0.37
Total protein (grams)	76.9 (48.2)	80.0 (36.4)	75.9 (51.7)	0.53
Glucose (grams)	25.2 (17.2)	30.3 (17.6)	23.2 (17.0)	0.01
Fructose (grams)	28.0 (20.3)	33.6 (20.5)	25.8 (20.3)	0.02
Sucrose (grams)	35.8 (22.5)	37.5 (24.5)	35.0 (26.3)	0.59
Fiber (grams)	16.1 (8.2)	16.4 (7.3)	16.0 (8.5)	0.78
Vegetables ^c (servings)	2.5 (1.9)	2.6 (1.8)	2.4 (1.9)	0.56
Fruits ^d (servings)	1.2 (1.0)	1.2 (1.0)	1.2 (1.0)	0.97
Grains ^e (servings)	5.0 (2.9)	5.0 (2.7)	5.0 (3.0)	0.87
Whole grains ^f (servings) ^g	0.8 (1.0)	0.6 (0.8)	0.9 (1.1)	0.06
Sugary beverages (grams)	328.5 (375.8)	428.7 (392.7)	289.6 (370.1)	0.02
Alcohol consumption (% to total kcal)	5.5 (7.8)	5.8 (8.4)	5.5 (7.6)	0.78
Dessert sweets (% to total kcal)	16.0 (9.6)	17.8 (10.2)	15.4 (9.4)	0.12
Glycemic load	110.7 (55.5)	118.5 (55.0)	107.6 (56.3)	0.24
Glycemic index	51.0 (4.3)	51.0 (3.7)	51.1 (4.5)	0.97

^aA detectable (> 0.1 ng/mL) and rising serum prostate-specific antigen (PSA) or receipt of androgen deprivation therapy within 2 years after the radical prostatectomy

^bGroup 1, AJCC prognostic stage group I; Group 2, AJCC prognostic stage group IIA, IIB, and IIC; Group 3, AJCC prognostic stage group IIIA, IIIB, and IIIC.

^cDaily servings of vegetables

^dDaily frequency of fruits and fruit juices

^eDaily servings of breads, cereals, rice, pasta

^fAverage daily servings of whole grain

^gPictures of portion sizes from 1/4 cup to 2 cups were provided to study participants to help them estimate serving sizes for all food items.

Table 3.

Pre-Diagnostic Carbohydrate Intake in 205 Men with Early-Stage Prostate Cancer and Odds of Treatment Failure^a After Radical Prostatectomy

	Detectable and rising PSA or ADT after surgery (n=52)			ADT after surgery (n=46)	
Carbohydrate ^b		OR ^c	95% CI	OR	95% CI
Total carbs (excluding fiber)					
	tertile 1	ref.		ref.	
	tertile 2	1.54	(0.52,4.62)	2.39	(0.77, 7.57)
	tertile 3	1.81	(0.59, 5.59)	2.72 [*]	(0.83, 8.80)
Total sugars					
	tertile 1	ref.		ref.	
	tertile 2	2.27	(0.72, 7.19)	5.38 ^{***}	(1.51 19.1)
	tertile 3	2.24	(0.70, 7.16)	4.03 ^{**}	(1.12 14.5)
Glucose					
	tertile 1	ref.		ref.	
	tertile 2	2.65 [*]	(0.83 8.45)	2.92 [*]	(0.89 9.58)
	tertile 3	2.51	(0.73 8.67)	3.09 [*]	(0.87 11.0)
Fructose					
	tertile 1	ref.		ref.	
	tertile 2	2.39	(0.74, 7.69)	3.53 ^{**}	(1.05 11.9)
	tertile 3	2.20	(0.67, 7.22)	3.23 [*]	(0.93, 11.2)
Sucrose					
	tertile 1	ref.		ref.	
	tertile 2	1.39	(0.47, 4.07)	2.73 [*]	(0.87, 8.52)
	tertile 3	2.60 [*]	(0.87, 7.76)	5.68 ^{***}	(1.71, 18.9)
Fiber ^d	grams/day	0.92 ^{**}	(0.85, 0.99)	0.88 ^{***}	(0.81, 0.96)

NOTE: PSA, prostate-specific antigen; ADT, androgen deprivation therapy; OR, odds ratio; CI, confidence interval.

^aDetectable (> 0.1 ng/mL) and rising serum PSA or receipt of ADT within 2 years after surgery.

^bCarbohydrate intake tertiles are based on the energy-adjusted residuals of the natural log-transformed nutrient intakes.

^cOdds ratios adjusted for age at diagnosis, race/ethnicity, body mass index, average daily total caloric intake, percent calories from alcohol, prognostic group, surgical margin status, and study site. BMI, prognostic group, and surgical margin status were independent predictors in all models evaluated (p < 0.001 to 0.006).

^dBased energy-adjusted residual intake without log-transformation.

^{*} 0.05 p < 0.1

^{**} 0.01 p < 0.05

^{***} 0.001 p < 0.01

Table 4.

Pre-Diagnostic Carbohydrate Intake Quality in 205 Men with Early-Stage Prostate Cancer and Odds of Treatment Failure^a After Radical Prostatectomy

Measure	Detectable and rising PSA or ADT after surgery (n=52)		ADT after surgery (n=46)	
	OR ^b	95% CI	OR	95% CI
Glycemic load				
tertile 1	ref.		ref.	
tertile 2	1.75	(0.55, 5.59)	2.48	(0.75, 8.19)
tertile 3	2.95	(0.68, 12.8)	4.52 [*]	(0.97, 21.1)
Glycemic index				
tertile 1	ref.		ref.	
tertile 2	1.27	(0.43, 3.81)	1.78	(0.58, 5.50)
tertile 3	2.19	(0.67, 7.17)	3.63 ^{**}	(1.05, 12.5)
<i>Intake quality scores</i>				
Low sugar/high fiber ^c (range, 0 to 8)	0.82 [*]	(0.67, 1.01)	0.83 ^{***}	(0.71, 0.97)
Low sugar/high fiber+low fat/high protein ^d (range, 0 to 12)	0.75 ^{***}	(0.60, 0.93)	0.78 ^{***}	(0.66, 0.92)

NOTE: PSA, prostate-specific antigen; ADT, androgen deprivation therapy; OR, odds ratio; CI, confidence interval.

^aDetectable (> 0.1 ng/mL) and rising serum PSA or receipt of ADT within 2 years after surgery.

^bOdds ratios adjusted for age at diagnosis, race/ethnicity, body mass index, average daily total caloric intake, percent calories from alcohol, prognostic group, surgical margin status, and study site. BMI, prognostic group, and surgical margin status were independent predictors in all models evaluated ($p < 0.001$ to 0.008).

^cThe sum of the tertile ranks of the energy-adjusted residuals for the natural log-transformed intakes of glucose, fructose, and sucrose plus the tertile rank of the energy-adjusted residual of fiber intake.

^dThe "low sugar/high fiber score" plus sum of the tertile ranks of total fat and total protein intake as a percentage of total calories. Lower intakes of sugars and fat and higher intakes of fiber and protein are associated with higher (i.e., better) scores.

^{*} 0.05 $p < 0.1$

^{**} 0.01 $p < 0.05$

^{***} 0.001 $p < 0.01$

Table 5

Associations Between Treatment Failure^a After Radical Prostatectomy and Pre-Diagnostic Intake of Fruits, Vegetables, Whole Grains, and Sweets in 205 Men with Early-Stage Prostate Cancer

Food Item	Detectable and rising PSA or ADT after surgery (n=52)		ADT after surgery only (n=46)	
	OR ^b	95% CI	OR	95% CI
Vegetables, ^c servings/day				
tertile 1	ref.		ref.	
tertile 2	1.08	(0.38, 3.05)	0.98	(0.35, 2.77)
tertile 3	0.99	(0.34, 2.92)	0.96	(0.32, 2.84)
Fruits, ^d servings/day				
tertile 1	ref.		ref.	
tertile 2	1.34	(0.49, 3.68)	1.01	(0.37, 2.79)
tertile 3	0.84	(0.28, 2.50)	1.00	(0.35, 2.86)
Whole grains, ^e servings/day ^f				
tertile 1	ref.		ref.	
tertile 2	0.74	(0.27, 2.03)	0.99	(0.37, 2.67)
tertile 3	0.30**	(0.10, 0.94)	0.57	(0.20, 1.65)
Dessert Sweets, % total kcal intake/day				
tertile 1	ref.		ref.	
tertile 2	1.17	(0.39, 3.52)	1.49	(0.50, 4.44)
tertile 3	3.58**	(1.19, 10.8)	3.47**	(1.16, 10.4)
Sugary beverages, grams/day				
tertile 1	ref.		ref.	
tertile 2	1.12	(0.35, 3.57)	1.98	(0.62, 6.32)
tertile 3	3.12*	(0.93, 10.5)	3.61**	(1.05, 12.4)

NOTE: PSA, prostate-specific antigen; ADT, androgen deprivation therapy; OR, odds ratio; CI, confidence interval.

^aDetectable (> 0.1 ng/mL) and rising serum PSA or receipt of ADT within 2 years after surgery.

^bOdds ratios adjusted for age at diagnosis, race/ethnicity, body mass index, average daily total caloric intake, prognostic group, surgical margin status, and study site. BMI, prognostic group, and surgical margin status were independent predictors in all models evaluated ($p < 0.001$ to 0.007).

^cDaily servings of vegetables

^dDaily frequency of fruits and fruit juices

^eAverage daily servings of whole grain

^fPictures of portion sizes from 1/4 cup to 2 cups were provided to study participants to help them estimate serving sizes.

* $0.05 < p < 0.1$

** $0.01 < p < 0.05$