EDITORIAL

A healthy diet, a healthy prostate? A brief commentary on the latest research on diet and prostate cancer

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With global estimates of 1.4 million new diagnoses per year, prostate cancer (PC) is the second most common cancer and the fifth leading cause of death in men [1]. Recognizing and reversing the negative impacts of modifiable risk factors continues to be vital for improving morbidity and mortality in PC patients.

As public opinion on diet is ever changing, novel questions about dietary regimens and supplementation, and their association with PC are being asked. Does the inflammatory potential of certain diets play any role in PC risk? Can carbohydrate restriction affect tumor growth? Are fasting-mimicking diets, which are effective in the management of type 2 diabetes and metabolic syndrome, safe for weight management in PC patients as well? And since most research on modifiable risk factors comes out of high-income countries, the risk factors for PC in low- and low-middle-income countries and dietary choices may not be the same, though to date this has been little studied. In addition, the search for a dietary supplement with preventative effects on PC has yet to yield favorable results [2]. Though clear evidence for recommended use is lacking, the search for PC prevention supplements continues with omega-3 fatty acids. Lastly, obesity is associated with the development of multiple chronic diseases, including coronary artery disease, hypertension, and diabetes [3, 4]. With the impact of obesity on health becoming a major problem globally, questions are also emerging. Does obesity increase the risk of PC? What is the relationship between obesity and biochemical recurrence (BCR)? Does weight management at initial diagnosis diminish the risk of BCR?

We address these questions in the current collection, which summarizes eight recent manuscripts on diet and obesity as modifiable risk factors for PC published from March 2021 to May 2022 in *Prostate Cancer and Prostatic Diseases*.

1. "Effects of dietary omega-3 fatty acids on orthotopic prostate cancer progression, tumor associated macrophages, angiogenesis and T-cell activation – dependence on GPR120" [5]. In an orthotopic MycCaP model, docosahexaenoic acid (DHA) supplementation reduced tumor growth in mice fed an omega-3 fatty acid diet compared to mice fed an omega-6 fatty acid diet. DHA also lowered infiltration of M2 macrophages, M2 macrophage-dependent angiogenesis and activation of T cells. These effects are thought to be partially mediated by GPR120. These data provide some mechanistic understanding of the potential of omega-3 fatty acids to modify the tumor microenvironment and thereby slow PC growth.
2. "Dietary Inflammatory Index and prostate cancer risk: MCC-Spain study" [6]. In a population-based case–control study including 928 PC cases and 1278 controls, cases had higher mean energy-adjusted Dietary Inflammatory Index (DII) values, although this difference was not statistically significant. Among cases, a pro-inflammatory diet, i.e., the third tertile of energy-adjusted DII, was associated with an increased risk of grade group 2 or higher PC risk. These data suggest that diets that promote inflammation may be linked with aggressive PC.
3. "Modifiable risk factors for prostate cancer in low- and lower-middle-income countries: a systematic review and meta-analysis" [7]. Higher vegetable intake and tea consumption were associated with lower PC risk while higher fat intake was linked with higher PC risk. There were non-significant trends for alcohol consumption, smoking, red meat intake, and a body mass index (BMI) of ≥25–30 kg/m^2 linked with increased PC risk. These data suggest that some of the same lifestyle factors linked with PC in western society may apply to other areas of the world too.
4. "The obesity paradox in metastatic castration-resistant prostate cancer" [8]. In a secondary analysis using data from the control arms of three phase III randomized trials of metastatic castration-resistant PC (mCRPC), obesity was associated with a lower risk of PC-specific and overall death. These data show that in contrast to findings in early-stage PC, obesity in late-stage PC could be a good prognostic sign, though the mechanisms of this are unclear.
5. "Serum metabolomic analysis of men on a low-carbohydrate diet for biochemically recurrent prostate cancer reveals the potential role of ketogenesis to slow tumor growth: a secondary analysis of the CAPS2 diet trial" [9]. In a secondary analysis of a randomized trial of low-carbohydrate diet vs. control in men with BCR, serum metabolomics showed that a longer PSA doubling time was associated with higher levels of 2-hydroxybutyric acids, ketone bodies, citrate and malate. These data point to the potential of ketogenesis and Krebs cycle metabolites to slow PC growth, though this requires more study.
6. "Comprehensive Lifestyle Improvement Program for Prostate Cancer (CLIPP) is associated with improvement in weight and components of metabolic syndrome in men exposed to androgen deprivation therapy for prostate cancer" [10]. Thirty-one PC patients treated with ADT received a 16-week curriculum on nutrition, physical activity, and self-support strategies followed by an 8-week period of passive support from a health coach in this single-arm unblinded clinical trial. Participants showed significant improvements in weight, waist circumference, blood pressure, and metabolic markers. The authors are planning a large-scale randomized clinical trial testing this curriculum.
7. "The impact of a fasting mimicking diet on the metabolic health of a prospective cohort of patients with prostate cancer: a pilot implementation study" [11]. Intermittent fasting for weight loss has been recommended for patients

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with chronic illness but has yet to gain widespread support for weight loss in cancer patients. This pilot prospective study enrolled 35 patients into 3 monthly cycles of a fasting-mimicking diet. With an adherence rate of 83% and no reports of safety issues, larger randomized control trials are surely warranted for this weight loss approach.

8. "Obesity and biochemical recurrence (BCR) in clinically localised prostate cancer: a systematic review and meta-analysis of 86,490 patients" [12]. Among surgical patients, but not patients treated with other modalities, obese patients (BMI ≥ 30 kg/m^2) had a higher BCR risk compared with normal weight patients (BMI < 25 kg/m^2) with risk increasing by 10% per every five units increase in BMI. Why results differed for surgical patients vs. other modalities is not clear and requires further study.

Although research linking diet and cancer is not new, recent studies suggest that dietary factors and obesity are associated with both PC risk and PC outcomes, thereby providing additional perspectives and mechanisms specific to PC.

For example, while omega-3 fatty acids and DII have been studied for several years, their role in PC is still not well defined. However, findings like those from Liang et al. and Lozano et al. bring insight into a novel mechanism by which DHA may exert benefit in PC and contribute to a growing body of evidence associating DII with PC risk, respectively [5, 6]. Evidence from this summary also leads us to conclude that fasting-mimicking and low-carbohydrate diets remain a "hot" topic in PC research. Once more, research on these interventions proves them feasible in multiple stages, as shown by patients with biochemically recurrent PC following a low-carbohydrate diet in Chi et al. [9]. However, larger clinical trials are still needed. In the two studies focused on obesity, obesity was defined by BMI. While the accuracy of BMI in predicting of obesity remains debatable, both studies provide additional evidence linking obesity with PC, including in advanced disease, where conflicting results exist [8, 12]. Unsurprisingly, the link between obesity and cancer remains context dependent, as it could help or hinder PC prognosis based on disease stage, as shown by these studies where a higher BMI was associated with BCR but higher survival in patients with mCRPC.

In summary, current research points to a myriad of singular factors that affect PC. However, questions remain as diet is a complex and longitudinal behavior. Ultimately, the key unanswered question remains: is it possible to construct an evidence-based diet for PC patients that reaches the trifecta, slows PC growth, improves quality of life, and is practical to implement with a high acceptance rate?

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GCG did the literature search, planning and wrote the manuscript. JPD, NAF and SD wrote the manuscript. SJF revised content, wrote the manuscript and approved the final version.

COMPETING INTERESTS

SJF is a consultant to Bayer, Sanofi, Astellas, Astra Zeneca, Pfizer, Myovant, Janssen, and Merck. The other authors declare that they have no conflict of interest.

ADDITIONAL INFORMATION

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