EDITORIAL

Clinical Research

# Plant-based diets to reduce prostate cancer risk and improve prostate cancer outcomes—ready for prime time?



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Intensive research has aimed to identify modifiable dietary factors to reduce prostate cancer (PC) risk and improve outcomes, but the evidence for these strategies remains inconclusive [1]. Plant-based dietary patterns, however, are emerging as appealing options with potential benefits that merit consideration. Historically, constituents in fruit and vegetables were studied to elucidate mechanisms linking their intake with reduced PC risk. While results from observational studies are encouraging, Level 1 evidence to support the benefits of specific constituents, plant-based dietary patterns, and plant-based foods is lacking [2].

In the current issue of Prostate Cancer and Prostatic Diseases, Gupta et al. [3] report a systematic review of the association between plant-based dietary patterns and PC risk and progression. Five intervention and 11 observational studies, published in 32 papers, were identified meeting the inclusion criteria. Of the 5 intervention studies, only two were randomized controlled trials (RCT), and all were small (<100 subjects), with short-term interventions (1-year or less). Interventions were not limited to diet but included stress reduction and/or meditation and/or exercise. Outcomes reported included prostate specific antigen (PSA), PSA doubling time (PSADT), circulating hormonal and lipid levels and nutritional adequacy of participants. While results suggested benefits from plant-based diets, given the limited sample sizes, short-term intervention, use of intermediate biomarkers and comprehensive lifestyle interventions vs just a plant-based diet alone, and the fact that only 2 were RCTs and one was a pilot trial, at best the conclusions may be viewed as supportive evidence to plan a larger scale intervention. Indeed, this was the conclusion from the two RCTs [4, 5] in this review.

Of the 11 observational studies, 7 were large cohort examining the associations between PC risk and vegetarian diets. Importantly, 5 of 7 cohorts reported null results, i.e., no association between plant-based diet and reduced PC risk. Two cohorts, the UK Biobank cohort, and the Adventist Health Study-2, reported reduced PC risks associated with vegetarian/vegan vs meat-eaters, and vegan vs lacto-ovo-vegetarian, pesco-vegetarian and semi-vegetarian diets, respectively, in multivariable adjusted models. Several case-control studies reported mixed results in men at various disease stages.

What are the take-home messages from this review? First, rigorously designed, well-powered RCTs are lacking. The Men's Eating and Healthy Living (MEAL) trial, a large RCT not included in this review, but mentioned in the discussion, remains the largest well-designed RCT to date testing the PC effect of increasing fruit and vegetable consumption vs. usual diet [6]. The 2-year trial of men on active surveillance found no benefits for PC progression assessed using changes in end-of-study PSA, PSADT and upgrading on follow-up biopsy. While this study shows adding more fruits and vegetables to a standard American diet has no PC-related benefit for men on active surveillance, how generalizable are these findings to plant-based diets?

This question leads to the second take-home message that diets considered to be "plant-based" vary widely. A recent review highlighted the broad spectrum of definitions, qualities and characteristics that encompass plant-based diets [7] from the extreme vegan diet to semi-vegetarian or "primarily plant-based" where some animal food consumption is allowed. Even the Mediterranean and DASH diets may be considered plant-based owing to their emphasis on plant-based products and the reduction of meat consumption [7]. As "plant-based diets" vary in health-related and potentially anticancer nutrients and constituents, it is imperative to be clear about the food composition of plant-based diets. For example, "the twinkie diet" [8], with the exception of eggs, would be considered plant-based. As such, there is a tremendous difference between whole foods plant-based diets and a twinkie-based diet, while both being "plant-based". This heterogeneity is also illustrated in one of the pilot trials reviewed by Gupta et al. [9], where the intervention is described as "an increase in plant-based foods and oily fish and a reduction or elimination of land-animal-based protein" while another was described as "low-fat vegan" [5]. In other words, a study that promoted oily fish intake was included in the review as evidence for the role of a plant-based diet.

A third take-home message is that plant-based diets, may vary with respect to highly processed or ultra-processed foods, which have been associated with increased PC risk [10]. Furthermore, heat-treatment (e.g., grilling, and roasting) during both plant-based and animal-based food preparation increases the potential to create advanced glycation end-products (AGEs). AGEs are compounds produced non-enzymatically from interactions between reducing sugars, free amino groups, nucleic acids and lipids in a process known as glycation and are emerging as risk factors for PC risk and progression [11]. Indeed, vegetarians have been reported to have higher intakes of crisps and pizza (ultra-processed foods also high in AGEs) than meat-eaters [12]. This further highlights that diet is extremely complex and thus simple terms such as "plant-based", while easy to understand, may not capture the complexity of a diet that would optimize prostate health.

Despite the limitations and challenges described above, many of which were highlighted by the authors, intriguing results from strict vegetarian and vegan diets suggestive of PC benefit warrant further investigation. In fact, recent results from the UK Biobank, published following the completion of this review report a 43% reduced PC incidence in men following a vegan and/or vegetarian diet vs. meat-eaters [12]. Also encouraging for plant-based diets

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are even more recent results from the Health Professionals Follow-Up Study (HPFS) reporting lower fatal PC risk associated with greater consumption of plant-based foods [13].

While only 1% of HPFS men and <2% of UK Biobank participants were classified as strict vegetarian or vegan, interest in plant-based diets is increasing [2]. That being said, other dietary approaches beyond plant-based have also suggested PC benefits including low-carbohydrate [14, 15], ketogenic diet [16], low-glycemic diet [17], and low-fat fish oil diet [18]. Given this, should we counsel men to alter their diets to include more plant-based foods for PC prevention in the absence of supportive evidence from rigorously designed RCTs? While the evidence regarding the optimal diet for prostate and overall health is unclear, hopefully by encouraging our patients to avoid certain elements of the typical Western diet (i.e., high simple sugar, high saturated fat, and high calories) we can move towards better health.

It appears that while a plant-based diet may have benefits for the prostate and overall health, other diets may have similar benefits. However, for reducing PC risk and improving post-diagnosis outcome, until evidence becomes available from rigorously designed RCTs—the jury is still out.

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## REFERENCES

1. World Cancer Research Fund/American Institute for Cancer Research: Diet, nutrition, physical activity and cancer: a Global Perspective. Continuous Update Project Expert Report: Diet, nutrition, physical activity and prostate cancer, 2018. Available at: dietandcancerreport.org (Last accessed: July 3, 2022).
2. Shah UA, Iyengar NM. Plant-based and ketogenic diets as diverging paths to address cancer: a review. JAMA Oncol. 2022;8:1201–8.
3. Gupta APH, Taylor J, Borin JF, Jacobsohn K, Kenfield SA, Eggener SE, et al. Systematic review of the impact of plant-based diet on prostate cancer incidence and outcomes. Prostate Cancer Prostatic Dis. 2022;25:444–52.
4. Ornish D, Magbanua MJM, Weidner G, Weinberg V, Kemp C, Green C, et al. Changes in prostate gene expression in men undergoing an intensive nutrition and lifestyle intervention. Proc Natl Acad Sci USA. 2008;105:8369–74.
5. Ornish D, Weidner G, Fair WR, Marlin R, Pettengill EB, Raisin CJ, et al. Intensive lifestyle changes may affect the progression of prostate cancer. J Urol. 2005;174:1065–9.
6. Parsons JK, Zahrieh D, Mohler JL, Paskett E, Hansel DE, Kibel AS, et al. Effect of a behavioral intervention to increase vegetable consumption on cancer progression among men with early-stage prostate cancer: the MEAL randomized clinical trial. JAMA. 2020;323:140–8.
7. Kent G, Kehoe L, Flynn A, Walton J. Plant-based diets: a review of the definitions and nutritional role in the adult diet. Proc Nutr Soc. 2022;81:62–74.
8. The Twinkie Diet. Available from: https://www.foodnetwork.com/fn-dish/behind-the-scenes/2017/01/food-network-staffer-diary-i-attempted-the-twinkie-diet-for-48-hours.
9. Carmody J, Olendzki B, Reed G, Andersen V, Rosenzweig P. A dietary intervention for recurrent prostate cancer after definitive primary treatment: results of a randomized pilot trial. Urology. 2008;72:1324–8.
10. Trudeau K, Rousseau MC, Parent M. Extent of food processing and risk of prostate cancer: the PROtEuS study in Montreal, Canada. Nutrients. 2020;12.
11. Krisanits BA, Woods P, Nogueira LM, Woolfork DD, Lloyd CE, Baldwin A, et al. Non-enzymatic glycoxidation linked with nutrition enhances the tumorigenic capacity of prostate cancer epithelia through AGE mediated activation of RAGE in cancer associated fibroblasts. Transl Oncol. 2022;17:101350.
12. Parra-Soto S, Ahumada D, Petermann-Rocha F, Boonpoor J, Gallegos JL, Anderson J, et al. Association of meat, vegetarian, pescatarian and fish-poultry diets with risk of 19 cancer sites and all cancer: findings from the UK Biobank prospective cohort study and meta-analysis. BMC Med. 2022;20:79.
13. Loeb S, Fu BC, Bauer SR, Pernar CH, Chan JM, Van Blarigan EL, et al. Association of plant-based diet index with prostate cancer risk. Am J Clin Nutr. 2022;115:662–70.
14. Freedland SJ, Howard L, Allen J, Smith J, Stout J, Aronson W, et al. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: carbohydrate and prostate study 1 (CAPS1) randomized controlled trial. Prostate Cancer Prostatic Dis. 2019;22:428–37.
15. Freedland SJ, Allen J, Jarman A, Oyekunle T, Armstrong AJ, Moul JW, et al. A randomized controlled trial of a 6-month low-carbohydrate intervention on disease progression in men with recurrent prostate cancer: carbohydrate and prostate study 2 (CAPS2) low-carbohydrate diet and prostate cancer progression. Clin Cancer Res. 2020;26:3035–43.
16. Lv M, Zhu X, Wang H, Wang F, Guan W. Roles of caloric restriction, ketogenic diet and intermittent fasting during initiation, progression and metastasis of cancer in animal models: a systematic review and meta-analysis. PloS One. 2014;9:e115147.
17. Lin DW, Neuhouser ML, Schenk JM, Coleman IM, Hawley S, Gifford D, et al. Low-fat, low-glycemic load diet and gene expression in human prostate epithelium: a feasibility study of using cDNA microarrays to assess the response to dietary intervention in target tissues. Cancer Epidemiol Biomark Prev. 2007;16:2150–4.
18. Galet C, Gollapudi K, Stepanian S, Byrd JB, Henning SM, Grogan T, et al. Effect of a low-fat fish oil diet on proinflammatory eicosanoids and cell-cycle progression score in men undergoing radical prostatectomylow-fat fish oil diet, serum eicosanoids, and prostate cancer. Cancer Prev Res. 2014;7:97–104.

## AUTHOR CONTRIBUTIONS

SF provided supervision, reviewed intellectual content and writing. IC planning and execution and writing. NF conducting research and writing.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

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