Editorial

Dietary intake and prostate cancer, continued pursuit for evidence

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The potential for diet to impact the risk and/or progression of prostate cancer (PCa) has inspired many research studies. Preclinical and human studies have examined the effect on PCa of nutrients and dietary factors including fat, protein, carbohydrate, fiber, vitamins, minerals and phytonutrients. Specific foods such as pomegranate, green tea, tomatoes and dietary patterns such as the Mediterranean and low carbohydrate ketogenic diets have also been examined in limited studies. Overall, some have shown a potential effect, however, most lack the confirmation by randomized controlled trials (RCT) in humans and thus the findings remain inconclusive (1).

In the 11/01/2018 issue of the *Prostate Cancer and Prostatic Diseases Journal* (2), Liss *et al.* reported that dietary total fat, saturated fatty acid (SFA), trans fatty acid (TFA), monounsaturated fatty acid (MUFA), cholesterol and vitamin E supplement are significantly associated with increased risk of PCa. In the large, population-based San Antonio Biomarkers of Risk (SABOR) cohort study, 1,903 men were enrolled from 2000 to 2010 and a baseline food frequency questionnaire was administered to assess dietary intakes. During a median follow up of 8.9 years, a total of 229 men were diagnosed with PCa by prostate biopsy. The authors examined if dietary intakes at baseline predicted future risk of PCa. Among all 133 nutrients analyzed, total fat, SFA, TFA, MUFA, cholesterol and vitamin E supplement showed a significant association with PCa, the higher the intake the greater the risk. Their finding is consistent with previous studies that also reported a direct association between fat intake, especially SFA, and risk of PCa (3-5). However, not all studies support an association of intakes of either total dietary fat, specific fatty acids or circulating levels of fatty acids and risk of PCa (6,7).

In preclinical studies using animal models, most generally show reducing fat intake slows the growth of PCa tumor (8-10). In addition, consuming diets high in fats, especially animal fat and corn oil, increase PCa progression (11). However, a diet high in fish oil (ω-3) significantly decreased PCa tumor volume and reduced gene expression in markers for M1 and M2 macrophages, related cytokines and chemokine CCL-2 (12). Another study directly compared four different *types* of fat including ω-3 (fish), ω-6 (corn), MUFA (olive), and SFA (animal) and found a high fish-oil (ω-3) diet significantly slowed PCa growth (13). Accordingly, fat type such as animal *vs.* plant source and specific fatty acids, rather than simply the total content of fat intake may be critical when examining the relationship between fat intake and PCa.

The potential mechanisms that a high-fat diet may influence disease progression in PCa include modulating fatty acid synthase expression (14) via increased proinflammatory cytokines (15), IGF-1 (16) and by reducing GPx3 expression and increasing the proliferation of prostate intraepithelial neoplasia epithelial cells (11). Studies also show that *de novo* lipogenesis is an important indicator for disease progression of PCa and blood indicators of *de novo* lipogenesis are positively associated with high grade PCa (17). Consuming diets high in total fat may also promote the infiltration of immune cells into prostate

tissues and the basal to luminal differentiation (18). However, despite the potential mechanistic linkage between dietary fat and PCa, research in human using rigorous RCT design, is scarce and largely inconclusive (1).

A meta-analysis that examined 14 cohort studies showed that there is no linkage between various fats (total, PUFA, MUFA, SFA) and either total PCa or advanced PCa (6), whereas other studies show that diets high in plant-based or ω-3 fats may be linked with a lower risk for PCa. A randomized control trial of a low-fat diet supplemented with fish oil led to decreased proinflammatory eicosanoids and cell-cycle progression score in men receiving radical prostatectomy (19). Nevertheless, research examining the effect of fish oil in PCa has not shown consistent results. The SELECT trial showed that men in the highest quartile of total long-chain ω-3 PUFA intake (20:5ω3; 22:5ω3; 22:6ω3) had a higher risk for PCa (low-grade, high-grade and total) (20). Another meta-analysis that included 5,078 case patients and 6,649 control patients from seven studies also reported that the highest intakes of eicosapentaenoic acid (20:5ω3) and docosapentaenoic acid (22:5ω3), was associated with a 14% and 16% greater risk in PCa, respectively (both $P<0.01$) (21). In addition, stearic acid (18:0), a SFA, was inversely correlated with total PCa risk. The association between intake of docosapentaenoic acid and PCa risk was significant for low-grade PCa only and not for high-grade disease. Thus, research of the association between fat and PCa risk or progression may require consideration of specific fatty acids and grade of PCa.

Indeed, the impact of diet on PCa may be influenced by the stages of disease. The patient population in Liss *et al.* was mostly low grade PCa which may be associated with different risk factors than those associated with more aggressive PCa. In fact, it is possible that many of the low grade PCa were detected due to an elevated PSA from an enlarged prostate (BPH) and the cancer was purely coincidental. For example, when the association between total fat, SFA, MUFA and PUFA was examined among 1,854 PCa cases in the North Carolina-Louisiana PC Project, both disease stage and race mattered (22). High SFA intake, adjusted for total fat intake, was associated with an increased odds ratio for aggressive PC with a suggestion of a stronger effect in men not using statins. High cholesterol intake, adjusted for total fat intake, was associated with aggressive PC in European Americans, but not African Americans. High PUFA intake, adjusted for total fat, was inversely associated with PC aggressiveness, even though this was not statistically significant. No associations were observed between MUFA or TFA intakes, total fat-adjusted, and PC aggressiveness, which differs from what Liss *et al.* reported. Hence, these two large observational studies support an association between SFA and PCa risk but the associations with MUFA, PUFA and TFA are inconsistent. Ultimately, any causal effect with SFA needs further verification with future RCTs.

Besides studying individual nutrients, there seemed to exist opportunity for the Liss *et al.* to examine the association between dietary patterns and risk of PCa with their data in future studies. This could potentially shed lights on the association between diet and PCa particularly in light of the fact that people consume whole foods in a dietary pattern and not just individual nutrients. Potential impact of dietary factors not captured by studying only individual nutrients may be missed. It is also possible that the inconsistent findings in fat and PCa among studies in humans may be explained by the lack of control over various dietary nutrients and factors related to PCa in a whole dietary pattern. Therefore, studying whole dietary pattern may reveal the integrated impact from all potential nutrients and factors. Previous research studies have examined the association between whole dietary pattern and PCa risk or progression. Consistent with the inflammation hypothesis for PCa, a proinflammatory diet was associated with a higher risk for PCa (23). Most recently, adherence to the Mediterranean and the DASH dietary pattern was reported to be associated with a lower risk for aggressive PCa (24). Similarly, the overall diet quality was examined in 1,191 participants diagnosed with cancer from the Third National Health and Nutrition Examination Survey (NHANES III). During a median follow-up of 17.2 years, a high-quality diet [highest-quartile Healthy Eating Index (HEI) score] was associated with decreased risk of overall and cancer-specific mortality when compared with a poor-quality diet (lowest-quartile HEI score). Thus, these research studies with "total diet" approach yield more consistent findings in diet and PCa (25).

In the above-mentioned study with NHANES III survey, the authors also reported that the highest-quartile score for SFA intake, thus a lower intake, was associated with decreased cancer-specific mortality (HR =0.55, 95% CI: 0.36 to 0.86). Further, iso-energetic substitution of SFA with MUFA and PUFA reduced all-cause and specific-cause mortality in US adults (26). Thus, a higher intake of total fat and particularly SFA may not only be associated with an increased risk for PCa, it is also associated with a higher overall mortality. Nevertheless, the impact of SFA intake on PCa risk and/or progression and particularly its

potential causal effect merits further research.

In the absence of definitive and compelling data, it is prudent to conclude that diet remains a promising factor toward PCa development and/or progression. According to the existing studies in human, a whole dietary pattern consistent with a healthy pattern like the Mediterranean and the DASH diets is associated with a lower risk for cancer specific mortality. These dietary patterns are also consistent with an anti-inflammatory dietary approach and with singular nutrient studies that showed a favorable association between a lower intake of SFA and higher intakes of specific antioxidant rich foods or nutrients. It is also possible that other diets that radically differ in their approach, but nonetheless lower inflammation such as a low-carbohydrate or ketogenic diet would have similar benefits (27). Indeed, some data support this hypothesis (28,29) and randomized trials are on-going (NCT01763944, NCT03679260).

While studying the association between specific nutrient or food factor with PCa is important for understanding the potential mechanistic pathways, a whole diet approach is practical for clinical implementation and for overall health management. As noted by the Liss *et al.* in their study, there was a dose-dependent relationship between fatty acids and risk of PCa. This supports that any change toward the "ideal" dietary pattern can convey health benefit and thus should be encouraged. Thus, dietary modification toward a healthy pattern like the Mediterranean or DASH for the benefit of PCa prevention and/or management and for overall health does not need to wait for the illumination of the causal roles of specific nutrient or food factors. Since PCa patients often carry an increased risk for cardiovascular disease already, effective strategies for dietary modification such as reducing SFA are likely to convey health benefit and also for PCa management.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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