Prostate Cancer Risk Connection to Immunity, Hormones, and the Microbiome

Jeffrey S. Bland, PhD, FACN, FACB, Associate Editor

Abstract

The evidence that diet and lifestyle play an important role in prostate health and disease is now clear. The clinical research indicates that a minimally processed, plant-food-based diet that is high in fiber, vitamins, and minerals, and includes diverse sources of phytonutrients is associated with improved prostate health and reduction in prostate cancer risk, as defined by PSA levels. A Mediterranean diet and the program developed and studied under the direction of Dr. Dean Ornish are two examples of effective approaches.

The mechanisms by which specific diet and lifestyle intervention improves prostate health are still under investigation. There is, however, increasing evidence that dietary components that favorably influence the composition of the intestinal microbiome have significant impact on androgen exposure to the prostate, and contribute to the reduction in both prostate cancer risk and progression.

Jeffrey S. Bland, ***PhD, FACN, FACB,*** *is the president and founder of the Personalized Lifestyle Medicine Institute in Seattle, Washington. He has been an internationally recognized leader in nutrition medicine for more than 25 years. Dr Bland is the cofounder of the Institute for Functional Medicine (IFM) and is chairman emeritus of IFM's Board of Directors. He is the author of the 2014 book* The Disease Delusion: Conquering the Causes of Chronic Illness for a Healthier, Longer, and Happier Life.

Prostate cancer is one of the most common forms of cancer in American men. After skin cancer, it is the second leading cause of cancer death in males. According to the National Cancer Institute and the American Cancer Society, more than 248 000 cases of prostate cancer were diagnosed in 2021, and one in eight men will receive a prostate cancer diagnosis during their lifetime. Although prostate cancer has a 5-year survival of more than 97% when properly diagnosed and treated, most men consider the prevention of prostate cancer to be a primary health goal.

A useful and widely accepted biomarker for assessing prostate cancer risk is, of course, prostate specific antigen (PSA).[1] Over the past decade, however, new biomarkers for improving the diagnostic accuracy of PSA have been developed.[2] The search for new biomarkers was prompted by the discovery that PSA can exist in multiple forms. Seventy to 90% of the PSA protein is complexed with serum protease inhibitors, while the remaining 10 to 30% exists in a free or unbound state. With this new understanding came the creation of the Percent Free PSA test, which is a ratio of free PSA to total PSA in the blood. In general, the lowest prostate cancer risk is associated with a Percent Free PSA value equal to or greater than 25%. The new recommendation is that men over the age of 50 have an annual evaluation of PSA and Percent Free PSA. The relative risk of prostate cancer increases with age, and therefore an important clinical variable is the rate of increase in PSA levels over time, with rapid increases indicating increased risk potential.

Lifestyle Intervention and Reduction of Risk to Prostate Cancer

In 2005, Dr. Dean Ornish and his colleagues at the University of California San Francisco published an important study suggesting that intensive lifestyle changes may affect the progression of prostate cancer.[3] This was small pilot trial involving men with prostate cancer who elected to follow a strict diet and lifestyle program, and the results reflected a reduction of PSA and improved prognosis of their prostate cancer. In a follow-up article published a year later, the same investigators reported that lifestyle and dietary intervention improved the quality of life of men with prostate cancer being managed with active surveillance.[4] This work continued, and in 2008 the team evaluated changes in prostate genetic expression in men with low-risk prostate cancer before and after initiation of an intensive nutrition and lifestyle intervention.[5] In this study, they found significant changes in gene expression after intervention that were indicative of improved metabolism and immune function. That same year, they published a two-year follow-up evaluation of the participants from an earlier study, and found that men with early-stage prostate cancer who chose active surveillance and implemented a healthy diet, exercise, and stress management program were able to avoid the need for conventional prostate cancer treatment.[6] Furthermore, men who had implemented the intensive nutrition and

lifestyle program were found to have increased telomerase activity, and—consequently—improved telomere maintenance capacity in immune cells.[7] In 2013, men with biopsy-proven, low-risk prostate cancer who had participated in previous studies of the comprehensive lifestyle and nutrition intervention were reevaluated, and the findings included longer term improvements in both telomerase activity and telomere length in immune cells, as well as improved health outcomes.[8]

Effects of Diet, Specific Nutrients, and Lifestyle on Prostate Health

Given the growing body of research demonstrating the positive impact an intensive nutrition and lifestyle program can have on prostate cancer, attention has now turned to identifying the mechanisms of action that influence prostate health. It is important to note that prostate cancer is driven by androgens (particularly testosterone), which explains why this condition is treated with androgen-deprivation therapies, including castration. Diet—both its impact on testosterone and its connection to prostate function—has long been an area of interest, and compelling studies examining this relationship are now emerging.[9]

Adherence to a Mediterranean diet has been associated with a reduction in prostate cancer risk, as well as a reduction in prostate androgens.[10] These effects are attributed to the type and balance of protein, carbohydrate, and fat (low in saturated fatty acids and higher in mono and polyunsaturated fatty acids) and also the abundance of certain phytonutrients. Omega-3 fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to improve immune resistance to prostate cancer in animal studies,[11] and specialized proresolving mediators (SPMs) derived from the metabolism of EPA and DHA have been shown to inhibit cancer cell proliferation through enhanced immune vigilance.[11,12] Phytonutrients that have specifically been found to be associated with the reduction in prostate cancer incidence include beta-sitosterol in legumes and oats, lycopene (a red carotenoid) in tomatoes, and oleuropein in virgin olive oil.[13] Both beta-sitosterol and lycopene have been found to influence testosterone dynamics through their impact on cellular signaling processes within the immune and endocrine systems.[14,15] In addition, numerous studies indicate that selective nutraceutical intervention with prostate-active phytonutrients can have a positive impact on the prevention of both benign prostatic hypertrophy and prostate cancer.[16,17]

Connection of the Microbiome to Prostate Cancer

It goes without saying that the gut plays a central role in all of the dynamics discussed thus far. Recently, our understanding of the mechanistic connection of diet to prostate health has taken a dramatic step forward with the recognition that intestinal microbial composition and activity influences the androgen-mediated risk to prostate cancer and elevated PSA.[18] These factors can also impact how cancer responds to therapy due to modulation of the immune and endocrine microenvironment of the tumor.[19] This has recently been demonstrated through studies showing that fecal microbial transplant (FMT) from responsive patients to melanoma patients may overcome resistance to immunotherapy.[20]

Speciation of the microbial community in the gut is a major regulator of androgen metabolism.[21] Interestingly, it has been found that the concentration of androgens in the intestinal contents can be more than 70 times higher than that in the serum. There is also a sexual dimorphism in the control of metabolism that regulates cell signaling processes, including endocrine hormone activities.[22] This may, in part, help to explain differences that are seen in autoimmune prevalence in females versus males.

Early-life microbial exposures determine sex hormone levels and modify progression to autoimmunity in animal models. In one mouse study, the transfer of gut microbiota from adult males to immature females altered the intestinal microbiome of the recipients, resulting in elevated testosterone and autoantibody production.[23] These effects were found to be mediated through the androgen receptor, which demonstrates that the composition of the intestinal microbiome alters sex hormone levels and serves to potentially regulate autoimmune disease later in life in individuals with high genetic risk. This phenomenon that connects sex differences to interactions among the intestinal microbiome, sex hormones, and immunity has been given a name by key researchers in this field: the *microgenderome*.[24]

What doors have been opened by these discoveries? In diseases that are associated with sex hormone imbalances such as prostate cancer, treatments with therapies designed to rebalance the intestinal microbiome, including the use of pre-, pro-, and synbiotics, may improve outcomes. New light has also been shed on how various steroid molecules are both synthesized and metabolized by the intestinal microbiome and how this process is gender-specific. Sex hormones that are produced endogenously by reproductive organs are transformed in the liver to conjugated derivatives that are then excreted into the intestinal contents in bile. Depending upon the composition of the intestinal microbiome, these conjugated sex hormones can then be deconjugated by specific microorganisms to yield active sex hormones that can be resorbed into the blood or biotransformed into new steroid molecules with different hormonal or immune properties.[25] One of the principal processes that results in deconjugation of androgenic and estrogenic hormones involves the enzyme beta-glucuronidase. Respected research compiled for the Human Microbiome Project GI database has revealed at least 112 novel glucuronidases in the gut microbiome.[26]

What insights can be gleaned from these complex discoveries? A study published in *Science* this year

demonstrated that bacteria within the intestinal microbiome can promote resistance to treatments for prostate cancer designed to reduce androgen impact on prostate and potentially make them refractory to anti-androgen therapy, including castration.[27] The findings are summarized this way: "We found that androgen deprivation in mice and humans promotes the expansion of defined commensal microbiota that contributes to the onset of castration resistance in mice. Specifically, the intestinal microbial community in mice and patients with CRPC was enriched for species capable of converting androgen precursors into active androgens." They continue: "Fecal microbial transplantation (FMT) from CRPC mice and patients rendered mice harboring prostate cancer resistant to castration. In contrast, tumor growth was controlled by FMT from hormone-sensitive prostate cancer patients and *Prevotella stercorea* administration. These results reveal that the commensal gut microbiota contributes to endocrine resistance in CRPC by providing an alternative source of androgens."

Clinical Implications

The evidence that diet and lifestyle play an important role in prostate health and disease is now clear. The clinical research indicates that a minimally processed, plant-food-based diet that is high in fiber, vitamins, and minerals, and includes diverse sources of phytonutrients is associated with improved prostate health and reduction in prostate cancer risk, as defined by PSA levels. A Mediterranean diet and the program developed and studied under the direction of Dr. Dean Ornish are two examples of effective approaches.

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Resveratrol is a phytochemical that is being widely studied for its physiological effects. In 2017, it was reported that men with metabolic syndrome who consumed resveratrol experienced alteration in many serum metabolites, which was indicative of its influence on intestinal microbial activity.[28] The authors of this study stated the following conclusions: "The affected pathways should be the focus of future clinical trials on resveratrol's effects, and perhaps particularly the areas of steroid metabolism and the gut microbiome."

An interesting 2014 study examined the influence of walnuts on prostate specific antigen levels, and reported that one of its principal phytonutrients, ellagic acid, is metabolized by specific members of the intestinal microbiome into urolithins A and B. Furthermore, these metabolites were found to down-regulate the mRNA and protein levels of both PSA and the androgen receptor in a prostate cell line. The data showed that the urolithins inhibit androgen receptor-mediated PSA expression at the transcriptional level. Additionally, the urolithins induced apoptosis in prostate cancer cells. In summary, the study indicated that the microbial metabolites of walnut ellagic acid, urolithins, attenuate the function of the androgen receptor by repressing its expression, which results in a down-regulation of PSA levels and induces apoptosis. This suggests that a diet rich in ellagic acid-containing foods, such as walnuts, in conjunction with the composition of the microbiome, could contribute to the prevention of prostate cancer through its effects on androgen metabolism in the prostate.[29]

The metabolism by the intestinal microbiome of ellagic acid to urolithins has also been explored in a prostate cancer model to determine the cellular impact of urolithin A and B on androgen receptor activity and prostate cancer cell viability. The results of a controlled mechanistic study concluded that colonic metabolites from the metabolism of specific polyphenols such as ellagic acid by the microbiome may contribute to the chemoprevention of prostate cancer through the consumption of a varied polyphenol-rich diet or composite polyphenol preparations.[30]

Taken as a whole these recent advances in understanding constitute powerful information for clinicians. The connection among the intestinal microbiome, dietary and lifestyle variables, and the modulation of prostate gland function through the immune and endocrine systems has been studied, demonstrated, and documented by evidence. This opens new doors within the field of personalized lifestyle medicine and provides a path forward for new clinical tools to reduce the risk of prostate cancer, as well as a potential reduction in PSA and improvement in Percent Free PSA.

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