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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Preventing aggressive prostate cancer with proven cardiovascular disease preventive methods

Mark A Moyad

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Cardiovascular disease (CVD) has been the number one cause of death in the U.S. for 114 of the last 115 years. Risk factors for prostate cancer have primarily mirrored risk proven risk factors for CVD, especially aggressive disease. Obesity, dyslipidemia, glucose intolerance, metabolic syndrome, unhealthy dietary habits or caloric excess, lack of physical activity, and inflammation are just some of these shared risk factors. The evidence also suggests proven CVD preventive measures are identical to prostate cancer preventive measures, especially in regard to aggressive disease. Thus, apart from lifestyle measures that can encourage optimal heart and prostate health there are potentially several dietary supplements that need to be avoided in healthy men because they may also increase the risk of prostate cancer. However, there are also several low-cost, generic, safe in the appropriate individuals, and naturally derived agents that could reduce prostate cancer risk, and these can be discussed and remembered utilizing the acronym S.A.M. (statins, aspirin, and/or metformin).

Cardiovascular disease (CVD) has been the number one cause of male death in the U.S. for approximately 114 of the last 115 years, only exceeded for a single year by the influenza pandemic in 1918.^{1–4} Lifestyle and dietary change for CVD prevention directly appear to apply to cancer prevention and most other prevalent diseases such as type 2 diabetes. Any lifestyle change that mitigates the risk of heart disease has clinical evidence; it could

reduce the risk of prostate cancer, especially aggressive disease, and parameters that increase the risk of heart disease increase the risk of aggressive prostate cancer.

HEART HEALTH MIRRORS PROSTATE HEALTH

The positive or negative behavioral or lifestyle changes associated with CVD and prostate cancer abound. For example, smoking has been associated with a higher risk of being diagnosed with prostate cancer in past meta-analyses,⁵ a higher risk of aggressive prostate cancer, and mortality from prostate cancer.^{6,7} Obesity is also associated with a higher risk of aggressive and fatal prostate cancer,⁸ and a higher risk of recurrence posttreatment.⁹ It is also plausible that obesity is associated with a lower risk of localized prostate cancer, and a higher risk of advanced disease.^{10,11} Regular vigorous exercise (approximately 3 h or more per week) is a profound potential strategy to reduce significantly prostate cancer death after diagnosis, and simultaneously reduce all-cause mortality to a similar degree (50%–60%) in these same patients compared to men that perform only 1 h or less exercise per week.¹² Past studies including a recent summary of 22 studies published over the past 12 years support the modest prostate cancer prevention effects of exercise.^{13–15}

The correlation between prostate cancer risk and hypertension and/or anti-hypertensive medications are currently weak.¹⁶ However, hypertension as part of a continuum of unhealthy parameters such as observed with metabolic syndrome (central obesity, dyslipidemia and insulin resistance) is becoming a potential risk factor for prostate diseases including cancer.¹⁷ Alpha-blockers, originally discovered for blood pressure control, are still one of those most effective

treatments for men with prostate issues (BPH) and lower urinary tract symptoms (LUTS) despite not having consistent positive or negative impacts on prostate cancer risk.^{18,19} The synergistic impact of exercise and diet has demonstrated blood pressure lowering effects similar to most anti-hypertensive drug classes.²⁰ Caloric reduction in overweight and obese patients with or without hypertension may also provide similar benefits.^{1,21}

MULTIVITAMINS/DIETARY SUPPLEMENTS

Some of the largest past prospective epidemiologic studies are suggesting a greater rate of aggressive and fatal prostate cancer when consuming more than 1 multivitamin a day, and a potential further increasing risk when other high-dose individual supplements are also utilized (selenium, Vitamin E and zinc).²² Men with a family history of prostate cancer appeared to experience the largest and most significant elevated risks of this condition. Other large male observational studies have found somewhat similar results with multivitamins and some individual supplements.^{23–25} Multivitamins are also replete in my experience with higher doses of B-Vitamins such as B12 and folic acid, which have also recently been found to potentially have no impact on health or increase the risk of prostate cancer from the largest and most recent meta-analysis of clinical trials.^{26–28}

Regardless, the only true phase-3 like multivitamin trial for cancer prevention was the Physicians' Health Study 2 (PHS2), which included over 11 000 health male doctors and utilized a low-cost daily single oral multivitamin (Centrum[®] Silver). This multivitamin had similar safety to placebo over 11 years, and significantly and modestly reduced the risk of total cancer risk in healthy men (primary endpoint) and

Department of Urology, University of Michigan Medical Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA.

Correspondence: Dr. MA Moyad (mammoyad@aol.com)

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cataracts (secondary endpoint). There was no significant reduction in prostate cancer incidence or mortality, but nonsignificant modest reductions were observed.²⁹⁻³¹ It is also interesting that the original Centrum Silver utilized during this trial from 1997 to 2011 is not the identical product offered to consumers currently because over time these nutritional formulations appear to change based on some science and marketing. Patient could be encouraged to utilize Centrum Silver or something close to the formula, which is detailed in the first clinical trial publication for overall cancer prevention but not prostate cancer prevention in those with and without a baseline history of cancer.²⁹

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was the largest dietary supplement trial ever completed in prostate cancer.³² It randomized over 35 000 men into four groups: high-dose Vitamin E (400 IU day⁻¹), high-dose selenium (200 mcg day⁻¹), Vitamin E and selenium, or placebo. The trial was terminated early after a median of 5.5 years due to a lack of efficacy, although at the time a nonsignificant ($P = 0.06$) increase risk of prostate cancer in the Vitamin E arm, and type 2 diabetes in the selenium group ($P = 0.16$) were observed. Still, participant follow-up continued (54 464 added person-years), which provided more clarity of the further health impacts after the cessation of these agents.³³ A significant ($P = 0.008$; HR = 1.17) increased risk of prostate cancer was observed in the Vitamin E group, and the increased risk with this individual supplement began to emerge after only 3 years and was found to be consistent for low- and high-grade disease types. The risk of Gleason 7 or higher disease was greater for the three intervention arms compared to placebo but did not reach statistical significance. The HR and P value for Gleason 7 and higher disease compared to placebo were 1.16 ($P = 0.20$), 1.21 ($P = 0.11$), and 1.23 ($P = 0.08$) for Vitamin E, selenium, and the combination, respectively. Additionally, members of the SELECT research team recently reported a significantly increased risk of aggressive prostate cancer in men replete with selenium before utilizing a selenium supplement.³⁴ This continues to raise concerns over adding antioxidants in large quantities for healthy individuals already receiving sufficient levels of these compounds (as argued previously) from other sources such as regular dietary intake.

Countless other dietary supplements are replete with their own issues in terms of prostate cancer prevention or treatment. For

example, Vitamin D in mega-doses may have some similar issues to Vitamin E or selenium. In the area of prostate cancer prevention, Vitamin D has not been impressive thus far. Several epidemiologic studies have found either no impact or a potentially increased risk of aggressive prostate cancer or total cancer at higher 25-OH Vitamin D blood levels.^{35,36} For prostate cancer prevention, the Vitamin D test may provide more harm than good until more clinical endpoints are followed in healthy individuals.³⁷ The latest Institute of Medicine (IOM) report should also be a reminder that despite the perception, the recommended intakes of Vitamin D have only increased by 200 IU (5 mcg) in most groups and Vitamin D supplements still have the potential to increase the risk of hypercalcemia and nephrolithiasis.³⁸

Vitamin D blood levels may also simply be a marker of healthy behavior.¹ Higher levels of systemic inflammation and greater burden of many diseases can inhibit Vitamin D synthesis rendering supplementation futile or meaningless in some cases. For example, a lean man, with a low cholesterol level that consumes fish and exercises regularly is more likely to have a higher blood level of Vitamin D compared to a physically inactive overweight or obese man with dyslipidemia and other heart unhealthy parameters.^{39,40} Patients should be reminded that improvement in heart healthy parameters could increase Vitamin D levels without or with additional smaller increments in supplementation. This moment represents an opportunity to emphasize heart healthy lifestyle changes first before increasing pill counts.

S.A.M. (STATINS, ASPIRIN AND/OR METFORMIN)

Clinicians could discuss countless advertised options for prostate cancer prevention, but since none are currently associated with consistent reduction and the clinical visit needs to be efficient and pithy another approach can be successful with patients. An ancillary pill in prostate cancer should be proven to be heart healthy, cost-effective, benefits need to outweigh the risks, and there should be a minimal chance that this agent interferes with proven conventional treatment. Thus, the list is short but three such interventions exist and arguably should be discussed and also referred to the patient's primary care doctor. The acronym S.A.M. (statins, aspirin, and metformin) should arguably receive the most initial attention (everything else is secondary in my opinion). All three of these agents are "natural" (statins were derived from yeast,

aspirin from willow bark, and metformin from the French Lilac), generic, heart healthy, low-cost and if a patient qualifies (benefit outweighs the risk) then there are arguably no other ancillary pills/supplements that have as much overall positive morbidity and mortality data. Some supplements may be able to mimic the activity of these agents and could serve as an alternative for drug intolerant patients (for example, red yeast rice supplements instead of a statin).¹

Lower lipid levels have been associated with a lower risk of aggressive prostate cancer,¹ and increases in HDL ("good cholesterol") may also be protective.⁴¹ Heart disease may increase the risk of prostate cancer from observations derived from two notable pharmacologic studies of prostate cancer prevention,^{42,43} and a variety of epidemiologic investigations.¹ Some of the largest observational studies have suggested a lower risk of aggressive prostate cancer with cholesterol lowering interventions even when controlling for multiple confounding variables.⁴⁴

Aspirin has been garnering an impressive amount of preliminary data as a potential anti-cancer agent, especially in the area of colorectal cancer prevention.^{45,46} However, the overall data also suggest a reduced risk of prostate cancer or aggressive disease with this agent.⁴⁷⁻⁵⁰ The ability of aspirin to further reduce prostate cancer-specific mortality in men receiving radiation or surgery has also garnered some preliminary research.⁵¹ If a benefit appears to be derived from aspirin it appears, as with statins that men with high-risk disease features or a more aggressive molecular profile consuming these products for longer periods of time (5+ years) are the ones most likely to benefit.⁵² Interestingly, the first large meta-analysis and systematic review of 39 studies (20 case-control and 19 cohort) of aspirin and prostate cancer was recently published and concluded with the following: "aspirin use is inversely related to prostate cancer incidence and PCa-specific mortality."⁵³ More recently, data from a large pharmacologic prostate cancer prevention trial (REDUCE) have demonstrated a significant reduction in total and high-grade prostate cancer with aspirin use.⁵⁴

Metformin is also beginning to demonstrate evidence as a cancer prevention or recurrence inhibition agent in those with and without diabetes and is currently in a phase-3 trial in breast cancer patients with survival as the primary endpoint.⁵⁵ A preliminary small phase-2 trial has suggested it may have the potential to slow the progression of even advanced prostate cancer (1000 mg

twice a day).⁵⁶ Additionally, a recent clinical trial of patients with prostate cancer on ADT for 6 months utilizing 850 mg twice a day of metformin with a suggested low glycemic diet (caloric restriction) were able to significantly reduce weight gain, BMI, waist circumference, and systolic blood pressure compared to the control group.⁵⁷ Men on metformin were also able to maintain glucose and HgbA1c levels. Metformin is cost-effective, safe, reduces weight gain, diabetes risk, and arguably CVD and perhaps total cancer and prostate cancer risk.^{1,58} Preliminary laboratory analysis also suggests that it may be synergistic with a variety of standard and nonstandard agents (including statins).^{59,60}

CONCLUSION

Patients should be encouraged to do whatever is practical and plausible to reduce their risk of CVD to as close to zero as possible. This should provide the greatest potential to not only reduce the risk of prostate cancer, but other disease morbidity and even impact all-cause mortality. Most major behavioral risk factors for CVD morbidity and mortality appear to be correlated with a higher risk of aggressive prostate cancer and/or fatal prostate cancer. The intention of S.A.M. is not to encourage patients to take one or all of these agents. It is to determine whether or not they already qualify for any of these agents based on their CVD risk. If they qualify the potential for a 2-for-1 or ancillary benefit should be emphasized. It is easy to become enamored by high-tech gadgets and costly agents or even costly dietary supplements, but it is the simplistic advice or changes that have profound impacts on CVD risk and it is beginning to appear as if prostate cancer prevention recommendations should emulate this historic example. In other words, “first do no harm.”

EDITORIAL COMMENT – (BY DR. JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

At the 2014 International Prostate Forum, two of our four themes included the very early spectrum of PSA screening and detection, specifically: (1) elevated PSA with prior negative biopsy, and (2) prostate cancer with low lethal potential. In both of these circumstances, the urologist's strategy for a patient may often lead to multiple visits for serial PSA trends and additional diagnostic tests. While I will assume that most urologists do not want to take over primary care duties for their patient, these clinical circumstances

certainly open the opportunity to compliment and reinforce healthy living habits and primary care strategies. Some urologists have promoted the concept of “Men's Health” initiatives^{61,62} and rightly point out our specialty's unique access to these opportunities.

For example, the urologist will likely see two types of patients on a regular basis where the true health-related needs lie beyond the PSA number or prostate cancer risk: (1) patients with obesity and other related co-morbidities who are seeking advice for elevated PSA or low-grade prostate cancer, and (2) patients who are interested (in some cases “interested” would be an understatement, i.e., already taking >5 supplements) in using dietary supplements to avoid prostate cancer and other health threats. In the first scenario, the evidence clearly shows that cardiovascular disease morbidity/mortality will outweigh their risk of being diagnosed with prostate cancer or dying of the disease. We must often still offer them the state-of-the-art in detection and treatment advice but always reinforce that long-term success will require a healthy heart. In the second scenario, the challenge is that there is so much information available for patients to read and often be misled into believing. It is possible that an individual patient can research and read more materials than his urologist! Hence, many urologists depend upon Professor Moyad and colleagues with similar expertise to help us find the most evidence-backed conclusions in this field of dietary supplements.

For patients in my practice, I have posed the question related to overall health and prostate cancer prevention: “where should I send you: the gym, the supplement store, or the pharmacy?” From Professor's Moyad's published books,⁶³ my takeaway messages have emphasized the answer is “the gym.” In this updated review, he reinforces the key evidence for the benefits of daily exercise, and shows where we may be headed in carefully selected daily vitamin use and/or the developing story of “SAM”: Statins, Aspirin, and/or Metformin.

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