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PROSTATE CANCER (S PRASAD, SECTION EDITOR)

Preventing Lethal Prostate Cancer with Diet, Supplements, and Rx: Heart Healthy Continues to Be Prostate Healthy and "First Do No Harm" Part I

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Abstract

Purpose of Review To discuss the overall and latest observations of the effect of diet, lifestyle, supplements, and some prescription heart healthy medications for prostate cancer prevention.

Recent Findings The concept of maximizing heart health to prevent aggressive prostate cancer continues to be solidified with the addition of more prospective observational and randomized controlled trial data. Heart healthy is prostate healthy, but heart unhealthy is prostate unhealthy.

Summary The primary goal of reducing the risk of all-cause and cardiovascular disease (CVD) morbidity and mortality also allows for maximizing prostate cancer prevention. The obesity epidemic in children and adults along with recent diverse research has only strengthened the nexus between heart and prostate health. Greater dietary adherence toward a variety of healthy foods is associated with a graded improved probability of CVD and potentially aggressive cancer risk reduction. Preventing prostate cancer via dietary supplements should encourage a "first do no harm", or less is more approach until future evidence can reverse the concerning trend that more supplementation has resulted in either no impact or an increased risk of prostate cancer. Supplements to reduce side effects of some cancer treatments appear to have more encouraging data. Medications that improve heart health including statins, aspirin, and metformin (S.A.M.), and specific beta-blocker medications are primarily generic or low-cost and should continue to garner research interest. A watershed moment in medical education has arrived where the past perception of a diverse number of trees seemingly separated by vast distances, in reality, now appear to exist within the same forest.

Keywords S.A.M. · Prostate cancer prevention · Cardiovascular disease · Diet

Introduction

A negative milestone with current and future individual health and health care system consequences was recently attained in the United States (USA). A 40% prevalence in adult obesity was recently noted, which is the highest number ever observed [1]. This obesity percentage is almost equaled by the number of overweight adults. It could now be argued that of every seven to eight of every 10 individuals visiting a physician today need to reduce their weight or waist size to improve their health. Additionally, the prevalence of teenage or young adult (age 12–19 years) obesity has reached a remarkable 20% or more prevalence, again the highest ever recorded in the USA [2•]. The majority of obese adults today were not obese as children, which suggests near future prevalence numbers will be even higher without immediate intervention.

These observations are cause for concern in the USA and in most other industrialized countries, along with fact that cardiovascular disease (CVD) is not only the current number 1 cause of death in men and women but it has also occupied this dubious position for more than 100 consecutive years. This observation alone attempts to place prostate cancer prevention in a more proper and manageable perspective for the clinician and patient [3••]. Approximately 159,000 individuals died of CVD last year that were younger than the age of 65, so CVD is not just a disease of the elderly as essentially 1 out 5 CVD deaths occur in middle-age or earlier. Young and older adult populations are becoming more metabolically or heart unhealthy, and this is one of the reasons why life expectancy in the USA recently decreased, reversing decades' long trend of improved survival.

This article is part of the Topical Collection on *Prostate Cancer*

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The positive news among the plethora of concerning data is that the nexus between prostate and heart health proffered well over a decade ago in this and other journals appear to no longer be theory or uncommonly utilized [4–6], but rather an accepted mantra entrenched in countless research since that time [7–9, 10•]. This is likely due to the acceptance and recognition of CVD posing a greater overall mortality risk for men in general or after a diagnosis of localized non-aggressive prostate cancer and has led to the utilization of heart healthy changes to reduce at least one or ideally both diseases (a "first do no harm lifestyle changes approach") (Table 1). Although the terminology utilized today may change or evolve (e.g., a greater "dietary inflammation index" being correlated with an increased risk of prostate cancer [11]), the general message remains identical and should be unified. The potential for heart health to reduce the risk of development or death from aggressive prostate cancer should continue to be highlighted as well as the impact of heart health on reducing the burden of multiple urologic diseases such as benign prostatic hyperplasia, bladder cancer, incontinence, and sexual dysfunction [12–14].

Fortunately, 80% of cardiovascular disease can be prevented by maintaining a healthy weight; improving dietary health; controlling dyslipidemia, hypertension, and diabetes; being more physically active; and not smoking. The greater number of heart health metrics achieved become tantamount to a graded and progressive reduced risk of cardiovascular and all-cause mortality [3••]. Thus, an emphasis on these heart healthy approaches should be encouraged to reduce the burden of prostate cancer.

Table 1 Partial list of novel and traditional potential risk factors and reducers associated with cardiovascular disease (CVD) and prostate cancer from recent and ongoing research.

Shared heart/prostate health lifestyle risk factors and reducers	Risk relationship commentary
Alcohol	Moderate to excessive intake increases aggressive disease and reduces efficacy of BPH medications. Large source of caloric excess and contribution to obesity that is still underappreciated.
Coffee	Could be causal or associated with lower risk, but lower caloric intake is generally favorable when analyzing beverage research (as is tea, for example, but fruit juice is more concerning in terms of caloric intake and weight management).
Dietary pattern (quality) Adherence (vegetables, fruit, legumes, fiber, non-processed, nuts, sees, minimal sugar, whole foods, low intake of red meat, processed meats)	DASH, Mediterranean, and other higher quality diets are associated with lower cancer and urologic conditions. Most of these healthy dietary patterns were first observed to profoundly reduce some aspect of CVD, and the greater the adherence, the greater the potential reductions (graded response).
Dyslipidemia	Appears to increase the risk of aggressive prostate cancer from preliminary research separate from metabolic syndrome criteria.
Hypertension	Part of metabolic syndrome associated with a greater risk of prostate cancer.
Inflammation (chronic)	Another synonym for "heart unhealthy is prostate healthy"
Obesity (and overweight)	May increase aggressive disease and reduce efficacy of BPH medications, and weight reduction is now needed in 7 to 8 of every 10 adult patients.
Physical inactivity/exercise	Exercise or cardiorespiratory fitness may slow the progression of prostate cancer, but minimal to no exercise appears to increase risk. More attention should be given to mental health benefits of exercise.
Pre-diabetes or glucose intolerance	Part of metabolic syndrome associated with greater risk
Smoking	Increase risk of aggressive disease including recurrence and mortality. Increases the risk of "clustering" making it more difficult to improve other lifestyle factors including diet.

This table contains modifiable risk increases and reducers, which is why age, and family history, for example, are not mentioned

Obesity

There is arguably no greater potential for all-cause morbidity and mortality compression than discussing the benefits of trying to achieve a healthy weight. For example, obesity and cancer risk is causally related to at least 13 anatomic sites including esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, breast, uterus, ovary, kidney (renal cell), meningioma, thyroid, and multiple myeloma [15]. Prostate cancer incidence has not been consistently associated with obesity, but this common observation belies the past and recent research of a greater correlation between increasing weight and more aggressive or lethal prostate cancer. More than 85 published studies, including at least 50 prospective investigations, have found a correlation between increasing BMI and mortality from prostate cancer.

Competing causes of mortality in obese men such as CVD may obscure the association between obesity and prostate cancer incidence and death [16]. The elevated blood volume and resultant hemodilution in PSA with increasing obesity may lead to a delayed initial identification of prostate cancer risk during screening, delay in diagnosis, and an ultimately a higher risk of lethal prostate cancer with greater weight gain [15, 17, 18]. The pathologic observation of increasing periprostatic white adipose tissue inflammation in men with a higher BMI is associated with an increased risk of unhealthy cardiovascular markers and high-grade disease [19]. The larger average prostate size in obese men may also potentially reduce the initial biopsy accuracy, which can underestimate the impact of larger weight on overall cancer incidence and delay diagnosis [20].

Is more evidence needed of the apparent relationship between weight gain and an increased risk of aggressive disease or cancer? Men who underwent bariatric surgery with subsequent significant weight loss demonstrate a profound reduced risk in all-cause and cardiovascular mortality as well as hormone-associated cancer risk [21, 22]. The associated extension in life expectancy, however, may lead to increased overall rates of prostate cancer diagnosis in men undergoing bariatric surgery as they are likely to live longer given the reduction in CVD mortality. This has been observed in breast cancer, where obesity is observed to be "protective" in younger age groups, but with increasing duration and age, it increases the risk of aggressive and life-threatening cancer [23]. For example, obesity is associated with a consistent increased risk of post-menopausal breast cancer (including triple-negative) and worse outcomes for all breast cancer subtypes—ultimately resulting in a worse prognosis upon diagnosis.

Alcohol

There is an apparent shift occurring in the research involving the health benefits of alcohol in moderation [24, 25•]. Numerous past publications identified the potential for improved cardiovascular outcomes with what appeared to be reasonable daily intakes. More recently, the literature suggests there could be no true safe intake of alcohol. Alcohol is considered a high-risk or potent carcinogen, and the lists of cancers associated with increased consumption, including male cancers, are expanding [26]. One of the most extensive meta-analyses conducted on the subject and prostate cancer risk has found a significant dose-response relationship, starting at low-volume intake [27]. Heavy drinking, defined as four or more drinks daily on five or more days a week, has been correlated with a significant increase in the risk of high-grade prostate cancer in the Prostate Cancer Prevention Trial (PCPT) [28•]. The REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial appears to have been impacted by alcohol use in a similar way. Men reporting moderate weekly drinking or greater were 86% ($p = 0.01$) more likely to be diagnosed with high-grade prostate cancer [29]. Alcohol may reduce the secondary benefits of 5-alpha reductase inhibitors, and if verified, leaves one to ponder other prostate medications that may be less efficacious with greater alcohol intake. Both trials (PCPT and REDUCE) also found a reduced efficacy for these medications in the management of BPH in the setting of obesity [30, 31]. Perhaps, there should be more attention placed on the negative synergism of alcohol, weight gain, BPH, and chemoprevention treatments in men.

Portion sizes and alcohol content are critical to evaluate by clinicians. If there are approximately 15 g of alcohol in standard traditional drinking portions (12 oz of beer at 5% alcohol, 5 oz of wine at 12%, or 1.5 oz at 40%), then what does this suggest for the increasing beverage sizes and alcohol contents currently witnessed? Will this lead to greater prostate cancer risk when consumption begins at younger ages and longer durations, as suggested by current studies [32]? The associated risk factor of increased caloric intake with greater volume of intake as well as the increasing alcohol by volume (ABV) of beverages correlates with male obesity or weight gain [33–35]. This observation in the setting of an ongoing obesity epidemic should alert health care professionals to discuss alcohol use alongside diet and lifestyle change. Simple math suggests that 2 or 3 larger-sized drinks (e.g., 16–20 oz beers) could contain the caloric equivalent of a daily meal (400–1000 cal). The amount of exercise and/or caloric reduction that would need to occur regularly to counter this effect is significant and leads to difficulty losing weight under these conditions for any patient that regularly consumes alcohol. This is further compounded by the fact that alcohol in excess produces an inflammatory state and encourages insulin resistance, accelerating adipose tissue accumulation [36].

Whereas prior studies have found an association of moderate or even higher alcohol intake with lower histologic evidence of BPH, increasing incidence or progression of LUTS has been noted with alcohol intake [37] including episodes of nocturia [38, 39].

Coffee, Tea, Pomegranate, Whole Fruits, and Vegetables

Coffee has enjoyed a resurgence in positive data suggesting greater intakes could be associated with a reduced risk of a plethora of medical conditions including all-cause and cardiovascular risk and mortality and certain neurologic and liver diseases [40]. Is it the coffee directly improving health of the individual, or is the average coffee consumer more likely to be healthier essentially giving the perception of a causal link that does not really exist? This correlation is not clear and may be influenced by the fact that most cups of coffee are lower caloric compared to other beverages such as alcohol or sugar-sweetened beverages which impact weight gain and development of obesity.

UK Biobank is arguably the largest population-based study of coffee consumption and caffeine metabolism and included almost half a million participants [41]. Researchers found similar health benefits in fast or slow metabolizers (genetic polymorphisms) as well as for instant, ground, and decaffeinated drinkers and summarized that coffee consumption is associated with a healthier lifestyle and that non-caffeine components in coffee could impact health more than caffeine. Recent large prospective studies of coffee consumption in patients with colorectal cancer demonstrated a significant reduction in recurrence and improved survival [42–46]; however, large prospective investigations suggest no or only a minor protective role of coffee and tea and prostate cancer risk and recurrence. It may be simply that the primary benefits are derived from coffee and tea serving as a lower caloric alternative to other beverage choices with a low incidence of adverse effects other than a possible increased risk of esophageal cancer with intake of higher temperature beverages such as coffee [47].

Other promising dietary products do not appear to have general efficacy in altering prostate cancer progression or risk [48–51]. While the early studies of pomegranate juice demonstrated some promise in prostate cancer prevention, subsequent randomized trials have been for the most part disappointing. In addition, higher caloric juices of any kind may contribute to weight gain, and juice intake has not been associated with weight loss. Therefore, clinicians need to be careful before recommending many fruit juice products not only due to the lack of favorable outcome data [52–54], and low- or no-calorie options are better choices for patients that continue to consume these drinks.

Increasing consumption of whole vegetables and fruit is associated with less weight gain and even weight loss [54, 55] but only in the setting of overall decreased caloric intake [56]. Patients should at least be educated on popular weight loss plans because they tend to share some common healthy instructions such as consumption of higher than normally required intake of vegetables as substitutes for unhealthy caloric dense foods or practices [57, 58].

There has been no long-term consistent observation of fruit and vegetable consumption per se lowering the risk of prostate cancer [59], but this may be confounded by rates of prostate cancer screening in healthier men. There has been a consistent finding of a reduced risk of prostate cancer with lycopene from multiple meta-analyses [60, 61], including a potential ability to inhibit angiogenesis in the tumor microenvironment of aggressive or lethal prostate cancer [62]. Plausible lycopene intake is simply a marker for greater or more diverse fruit and vegetable intake or a healthier overall lifestyle. Regardless, since one of the first strong prospective associations with lycopene and prostate cancer risk was published with a reminder that lycopene consumption and fruit and vegetable consumption are interdependent [63], it is remarkable that this correlation continues to remain strong in the literature. Clinicians and patients should also remember that lycopene and fruit and vegetable intake continues to demonstrate a reduced risk of CVD [64].

General Dietary Pattern Adherence (Quality) over Individual Dietary Components

It would be simplistic at this juncture to review every notable specific or individual food or nutrient that has been associated with CVD risk reduction that shares a simultaneous potential reduction in prostate cancer risk. For example, legumes have demonstrated this association in larger studies [65–68], but the ability of these dietary agents to reduce all-cause and CVD mortality is sufficient enough data to recommend them to patients with a desire to also improve their prostate health [69, 70].

Identifying whether it is the fiber from these healthy food sources that is responsible for a dual disease risk reduction [71] should not be the focus of extended efforts; the greater focus should be on identifying and advocating for the overall and consistent health benefit for patients that focus more on a dietary pattern rather than a micro-dissected specific nutrient. Numerous themes echo in the literature, which has shifted the thought process in cardiovascular disease prevention from specificity to generality when dealing with diet. For example, vegetables, fruits, whole grains, legumes, nuts, seeds, fish, perhaps some dairy, and low-to-moderate meat intake has been associated with a reduction in blood pressure in randomized trials [72]. Over time, these patterns are associated with

greater generalized disease reduction and the potential for better quality and quantity of life.

The Dietary Association to Stop Hypertension (DASH), for example, has arguably accumulated more general health benefits from an initial randomized clinical trial to reduce blood pressure than most dietary interventions [73•, 74, 75]. Remarkably, this trial demonstrated a reduction in blood pressure equivalent to modern day blood pressure medications in a diverse group of high-risk adults. DASH promoted the intake of fruits and vegetables, legumes, nuts, low-fat dairy, poultry, fish, whole grains, and some oils and recommended reduction of red meat intake, total fats, dessert, sweets, and sugar-sweetened beverages. This led to an emphasis on foods with greater fiber, potassium, magnesium, calcium, and protein and less of an emphasis on foods with sugar, cholesterol, saturated fat, and refined or processed products. It was not primarily designed to demonstrate ancillary non-cardiovascular health benefits, but more than two decades since initial publication, the impact on kidney stone reduction, weight loss, and the risk of some potentially lethal cancers appears profound [76–82].

The Mediterranean diet is often misunderstood as an extreme focus on olive oil rather than as another dietary pattern. It comprises moderate-to-high intake of vegetables, fruits, legumes, nuts, seeds, whole cereals, potatoes, and non-processed foods in general and low-to-moderate intake of sugar, red or processed meat, and animal foods including dairy, eggs, fish, and poultry along with alcohol in moderation with meals [83]. Adherence to the Mediterranean dietary pattern has been associated with numerous health benefits, especially CVD risk and mortality reduction [83], as well as a reduced risk of lethal prostate cancer [84•].

Again, there are numerous dietary patterns established from a variety of healthy cultures from around the world, as well as consistent behaviors in clinical trials utilizing these diverse diet options to promote better overall health. Improved quality and quantity of life have been associated with a higher number of healthy dietary changes (diet quality) [85]. DASH, Mediterranean, Nordic, and numerous other healthy dietary pattern initially were studied in the setting of CVD with ancillary benefits in cancer and other diseases identified subsequently.

Miscellaneous (Clustering, Ripple Effects, Smoking Cessation, Exercise)

If improvements in the quality of overall diet have the potential for such profound health changes, then it would suggest that any other lifestyle changes could be added to a dietary pattern to provide synergistic benefits. For example, there is enough comprehensive evidence to demonstrate the negative effects of smoking on the risk of most major chronic diseases. However, the newest member to this list should be prostate cancer since the potential to harbor aggressive disease, experience recurrence, and increased mortality can be considered causal rather than just correlated [86–88] with a reduced adherence to a higher quality diet. Indeed, positive as well as negative momentum effects abound when dealing with human health and lifestyle factors. This is known as "clustering" of health risk behaviors [89], and patients should be educated on this well-known but less-appreciated observation because this phenomenon is bidirectional and can be destructive as well as constructive. For example, smoking cessation is associated with improvement in diet and exercise status.

Data suggesting a reduced risk of aggressive prostate cancer diagnosis, progression, and mortality with exercise are accumulating [90•, 91–93]. The diverse impact of exercise on mental and physical health, improving mood, optimism, reducing stress, and anxiety levels is enough of a reason to recommend physical activity before even addressing the physical health benefits or the potential ability to reduce lethal prostate cancer. Regardless, when consulting on any aspect of exercise, diet, or even weight loss, there should be some discussion on the "ripple effect" [94•], which continues to demonstrate when one partner or spouse moves in a healthier direction then the other one is significantly more likely to move in that same direction. This is part of the unsung story of lifestyle changes as it relates to disease prevention.

Conclusion

The cardiovascular links to prostate cancer prevention appear to be almost endless [95]. For example, the ongoing research with metabolic syndrome increasing the risk of prostate cancer is just another reminder that "heart unhealthy is prostate unhealthy," but "heart healthy is prostate healthy." Cardiovascular markers indeed share a nexus with prostate cancer risk and arguably some forms of aggressive or lethal prostate.

The awareness of the association between cardiovascular and prostate health has not quite reached the attention recently observed in breast cancer where the American Heart Association (AHA) detailed the striking risk factor association between the two conditions [96•]. More research and publication are needed to improve the education level of the consumer, patient, and health care professional about these relationships. Prostate cancer risk reduction or risk factors should arguably be addressed next by the AHA since the correlation as demonstrated in this and countless other publications is as robust as breast cancer. The idea that cancer risk reduction through diet and other lifestyle changes is somehow independent of CVD risk is quickly becoming an antiquated thought process. A watershed moment in medical education has arrived where the past perception of a diverse number of trees seemingly separated by vast distances, in reality, now appears to exist within the same forest.

Compliance with Ethical Standards

Conflict of Interest Mark A. Moyad Abbie Speakers bureau on Diet Consultant for Farr Labs and max International.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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