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The Evolving Role of Diet in Prostate Cancer Risk and Progression

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Abstract

Purpose of review: This overview examines the rationale for dietary interventions for prostate cancer by summarizing the current evidence base and biological mechanisms for the involvement of diet in disease incidence and progression.

Recent findings: Recent data have further solidified the association between insulin resistance and prostate cancer with the homeostatic model assessment of insulin resistance (HOMA-IR). Data also show that peri-prostatic adipocytes promote extracapsular extension of prostate cancer through chemokines, thereby providing a mechanistic explanation for the association observed between obesity and high grade cancer. Regarding therapeutics, hyperinsulinemia may be the cause of resistance to PI3K inhibitors in the treatment of prostate cancer, leading to new investigations combining these drugs with ketogenic diets.

Summary: Given the recently available data regarding insulin resistance and adipokine influence on prostate cancer, dietary strategies targeting metabolic syndrome, diabetes and obesity should be further explored. In macronutrient-focused therapies, low carbohydrate/ketogenic diets should be favored in such interventions due to their superior impact on weight loss and metabolic parameters and encouraging clinical data. Other nutrients, including the carotenoid lycopene which is found in highest concentrations in tomatoes, may also play a role in prostate cancer prevention and prognosis through complementary metabolic mechanisms. The interplay between genetics, diet and prostate cancer is an area of emerging focus that might help optimize therapeutic dietary response in the future through personalization.

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Keywords

Diet; Prostate Cancer; Peri-prostatic Fat; Adipokines; Metabolic Syndrome; Ketogenic; Lycopene

Introduction

Prostate cancer ranks second in global cancer incidence and fourth in cancer mortality among men worldwide [1]. As a disease of aberrant growth, prostate cancer is heavily influenced by cellular growth signals. Many tumors, including prostate cancers, are associated with metabolic syndrome and insulin resistance, suggesting a dietary factor for this group of diseases [2-5]. Elevated body-mass index (BMI), an element of metabolic syndrome, correlates strongly with prostate cancer mortality [6]. Elevated BMI is also a risk factor for the progression of low grade to high grade prostate cancer [7]. The homeostatic model assessment of insulin resistance, or HOMA-IR, has now been shown to be associated with prostate cancer risk in a recent meta-analysis, with previous studies showing obesity correlating with higher grade and Gleason score at diagnosis, as well as higher recurrence rates and poorer prognosis [8-10]. However, diabetes, another aspect of metabolic syndrome, has often been shown to be protective against prostate cancer development [11]. Given the relationship between diet and metabolism, in this review we will first examine the influence of metabolic syndrome components on prostate cancer, followed by mechanistic explanations and a discussion of dietary interventional strategies.

Metabolic Disease and Prostate Cancer

Several studies have examined the impact of various components of metabolic syndrome and their effect on prostate cancer. Data from the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) revealed a strong association between metabolic syndrome and the incidence of high grade prostate cancer [12]. In this study, 8122 men were randomized to placebo or dutasteride following a negative prostate biopsy. Patients then underwent biopsies at 2 and 4 years, with BMI, hypertension, hypercholesterolemia, and diabetes risk factors recorded. Study results revealed that the presence of 3 or more metabolic syndrome components was significantly associated with increased risk of high grade prostate cancer (OR 1.94, $p=0.017$).

A number of investigators have examined the specific impact of diabetes on prostate cancer, with mixed results. In the case-control, population-based Prostate Testing for Cancer and Treatment (ProtecT) trial completed in the U.K., 1,291 men with biopsy confirmed cancer were compared to 6,479 matched controls from a group of 55,215 men enrolled in the study. Results from this analysis actually showed a reduced risk of prostate cancer with type 2 diabetes mellitus (T2DM) (OR 0.78, CI: 0.61-0.99) [13]. However, a recent analysis in over 1 million men in Israel revealed an increased risk of prostate cancer incidence during the first year after a diagnosis of diabetes, with a HR of 1.65 (CI 1.55-1.76) [*14]. Interestingly, the hazard ratio fell below one after two years, and stayed below one for the first 10 years after diabetes diagnosis. This suggests that treatment of diabetes may have a meaningful impact on prostate cancer development, and may also help explain the conflicting data [15]. It is of

interest that the T2DM drug metformin has been observed to have potential positive effects against prostate cancer and may reverse or impair resistance to ADT [16]. In a recently published systematic review of this topic, Crawley et al. contend that the balance of the available data indicates a negative effect on overall mortality in patients harboring both prostate cancer and diabetes [11].

Obesity has also been linked with prostate cancer progression. In a study of 565 men from Canada, men undergoing active surveillance were found to have a 50% increase in prostate cancer progression for every 5 point increase in BMI over 25 [7]. A meta-analysis demonstrated that obesity was particularly associated with an increased risk of aggressive prostate cancer (RR 1.14, 95% CI: 1.04 – 1.25) [17]. With respect to hypercholesterolemia, data from the prospective CLUE II study showed a lower incidence of high grade prostate cancer with low total cholesterol (<200 mg/dl) compared to high total cholesterol (>240 mg/dl) among men with elevated BMI (HR 0.36, p =0.02) [18].

Hormonal Mechanisms in Prostate Cancer

Testosterone is highly implicated in the growth of prostate cancer [19]. Anti-androgen therapy (ADT), a mainstay of prostate cancer treatment, works by lowering levels of endogenous testosterone. However, ADT also induces hyperglycemia and hyperinsulinemia [20-22]. Insulin and insulin-like growth factor (IGF-1) act on cellular signaling cascades to promote states of abundance and growth, including prostate carcinogenesis [19,23]. Additionally, androgens upregulate the IGF-1 receptor, which may further enhance aberrant growth [24]. One of the mechanisms of castration resistance may be due to the induced hyperinsulinemia from the reciprocal crosstalk between the androgen-insulin axes. This possibility presents a unique opportunity for dietary intervention, as will be discussed in this review below [22]. Finally, increasing evidence suggests that prostate cancer cells eventually utilize de novo steroidogenesis to maintain elevated local androgen concentrations [25]. High circulating insulin may enable or enhance de novo lipogenesis by way of upregulating the expression of multiple critical enzymes involved in lipogenesis [5]. Since over 50% of men will develop metabolic syndrome with long term ADT, these findings suggest a potential role for dietary therapy in reducing prostate cancer associated morbidities [26].

Prostate cancer cells, like many tumors, frequently have dysregulation in the PI3k-AKT-mTOR pathway and were shown to undergo apoptosis during mTOR inhibition [27]. Therefore, mTOR inhibition, whether by limiting insulin secretion and binding via dietary therapy, or blocking downstream signaling via pharmacotherapy, presents a promising avenue for future treatments.

Metabolic Mechanisms in Prostate Cancer

Mechanisms of carcinogenesis and disease progression in prostate cancer must be examined with an understanding of the unique metabolic features of normal, differentiated prostate cells. Unlike most tissues in the human body, prostate tissue is primarily glycolytic instead of oxidative. In fact, oxidative phosphorylation is disrupted at baseline by overexpression of the zinc-regulated transporter/iron-regulated transporter-like protein (ZIP1), which triggers

high zinc concentration within the normal cells and subsequent inhibition of m-aconitase, an enzyme in the tricarboxylic acid (TCA) cycle. The inhibition of m-aconitase prevents the conversion of citrate to isocitrate to permit greater concentration of citrate in prostatic fluid. Transformation into cancerous phenotypes entails an initial switch to oxidative phosphorylation due to loss of ZIP1 activity and thus zinc inhibition of m-aconitase [28,29].

The impact of insulin resistance on prostate cancer is theorized to occur through a few potential mechanisms. Hyperinsulinemia and insulin resistance may increase prostate cancer risk by increasing IGF-1 through reduction of IGF binding protein-1 [30]. Both HOMA-IR and the insulin-to-glucose ratio have been associated with an increased risk of prostate cancer. In addition, higher grade cancers appear to have more insulin receptors than lower grade tumors [31], indicating a possible explanation for the adverse impact of T2DM in more advanced tumors.

With respect to obesity, recent data suggests that peri-prostatic fat volume (PPFV) correlates positively with a greater risk of high grade cancer, and may be more important than BMI as a prognostic indicator. In a Dutch study of 932 patients treated with radiation therapy for T1-3N0M0 prostate cancer, higher PPFV was associated with a greater risk of harboring Gleason 8-10 cancer, T3 disease, or having initial PSAs > 10 ng/mL ($p < 0.001$) [32]. Furthermore, researchers from Scotland demonstrated that quantification of PPFV predicts for response to ADT independently of BMI. In their analysis, PPFV was significantly higher in patients who developed castration resistant prostate cancer compared to those who maintained a sustained response to ADT (median PPFV 37.9 cm³ vs 16.1 cm³, respectively; $p < 0.0001$) [33]. Recent data demonstrates that peri-prostatic adipocytes support the directed migration of prostate cancer cells through secretion of the chemokine CCL7 [34]. CCL7 produced by adipocytes diffuses into the peripheral zone of the prostate and promotes the migration of tumor cells. Obesity leads to elevated secretion of CCL7 and extra-prostatic tumor extension.

Another potential mechanistic concept combining both pharmacologic and dietary interventions was recently described in a study by Hopkins et al [35]. The basis of this strategy is that insulin-activated phosphatidylinositol-3 kinase (PI3k) is one of the signal transducers in the IR-PI3k-AKT-mTOR pathway, and is frequently dysregulated in many human cancers, including prostate tumors [36]. Indeed, dysregulation in this pathway was more common in cancers with significant hormone receptor overexpression, suggesting further interplay between these hormonal axes [36]. Given these mechanistic discoveries, PI3k inhibitors are an exciting pharmacologic choice for cancer therapy. However, they have been largely underwhelming in clinical trials, with the development of hyperglycemia and hyperinsulinemia as adverse events. Hopkins et al. demonstrated compensatory hyperinsulinemia as a likely mechanism by which resistance to PI3k inhibitors develops since this can be enough to overwhelm the pharmacologic blockade of the pathway. The compensatory insulin response was shown in prostate cancer cell lines in vitro. The group went on to combine a PI3k inhibitor with metformin, as well as a SGLT-2 inhibitor, and a ketogenic diet in vivo in other tumor models. In these experiments, the ketogenic diet limited insulin release as measured by C-peptide. Consequently, the combination of the PI3k inhibitor and ketogenic diet resulted in significantly decreased levels of tumor proliferation.

Upregulated anaerobic glycolysis, even in the presence of significant oxygen supply, was initially described by Otto-von Warburg and is one of the hallmarks of carcinogenesis [37]. A recent paradigm shifting hypothesis was proposed by Vander Heiden et al. suggesting the upregulation of glucose intake is not for the purpose of energy but for the accumulation of biosynthetic precursors for rapidly dividing cells [38]. Indeed, PI3k/AKT activate glycolytic enzymes. Drugs that block glycolytic enzymes, such as 2-deoxyglucose (2-DG) and 3-bromopyruvate (3-BP), were shown to cause prostate cancer cell death in preclinical models in combination therapies. The addition of 2-DG with metformin in one study, or with chloroquine in a second study, resulted in apoptosis of prostate cancer cell lines [39,40]. In a third study, 3-BP alone showed rapid prostate cancer cell death, likely due to its multiple effects on glycolytic flux [41]. To our knowledge, there is one phase I/II clinical trial using 2-DG in prostate cancer, which assessed patients with prostate cancer who took 2-DG for 14 days; the study showed competitive inhibition of glucose uptake with few grade 3 or 4 toxicities [42]. Combination therapies of diets that limit metabolite precursors of biomass production and pharmacologic substrate inhibitors, such as glycolytic inhibitors or glutamine inhibitors, have yet to be studied in clinical trials.

Epigenetic Impact of Dietary Metabolites

Recent studies link metabolites to direct epigenetic changes, including chromatin remodeling, DNA methylation, and histone modification [43]. These induced changes can even be passed to offspring as stable genetic expression patterns [43]. Histone deacetylases alter gene regulation, and high activity is associated with malignancy, including high expression in prostate cancer, and correlated with worse clinical outcomes [44]. Therefore, pharmacologic histone deacetylase inhibitors (HDACi) have been a recent promising addition to potential therapeutic targets, though none have progressed past phase II prostate cancer clinical trials due to little clinical effect noted to date [45,46]. Nevertheless, HDAC inhibitors comprise a promising area of future research. Recent studies show beta-hydroxybutyrate (BHB), a ketone body that circulates at physiologic levels in dietary ketosis, is a class I HDACi, reducing oxidative stress via gene repression in mice [47], though the efficacy of this mechanism has not been specifically demonstrated in prostate cell lines. HDAC inhibition via dietary metabolites remains another method by which cancer therapies could synergize with diet.

Small molecules within food, including a wide variety of micronutrients such as curcumin in the spice turmeric, sulforaphane in broccoli sprouts, and resveratrol in red wine, also induce epigenetic changes that may benefit health [48]. Lycopene, the most thoroughly-studied micronutrient pertaining to prostate cancer prevention and prognosis, is discussed further below.

Dietary Interventions

The history of dietary manipulation in cancer therapy is well over a century old, with the first published studies attempting to influence tumor growth conducted in the early 20th century in Germany [49]. Many observational and clinical studies have since been conducted demonstrating robust associations between diet and cancer. We present data on both

macronutrient-focused (low-carbohydrate and ketogenic diets) and micronutrient-focused (lycopene) approaches to prostate cancer prevention and treatment.

Macronutrient Interventions

It is well known that caloric restriction lowers circulating insulin and decreases insulin resistance^[50]. This may be one of the mechanisms by which caloric restriction imparts benefit in cancer patients, particularly those with elevated BMI. Low carbohydrate or very low carbohydrate/relatively low protein ketogenic diets may also reduce circulating insulin levels. At least two clinical trials have tested insulin sensitivity while comparing very low carbohydrate with low fat diets, and both showed superior improvements in insulin sensitivity in the low-carbohydrate arms^[51,52]. Furthermore, the most recent meta-analysis of low-carbohydrate clinical trials, with low carbohydrate intake correctly defined as less than 20% of caloric intake, showed a higher net weight loss with low-carbohydrate interventions^[53]. These findings suggest that overall caloric restriction, and perhaps more specifically, carbohydrate restriction, may benefit cancer patients through the reduction of insulin signaling.

The ketogenic diet is a subset of the broader class of low-carbohydrate diets. Ketogenic diets are very low carbohydrate, low protein, and very high fat diets distinguished by induction of ketosis, defined as the presence of ketone bodies in the blood stream. The classic implementation of the ketogenic diet consists of a target ratio of 4 to 1 of caloric intake from fat to combined carbohydrate plus protein. However, this ratio may not be necessary for some individuals and inclusion of increased medium-chain triglycerides, often derived from coconut or macadamia nut oils, is believed to promote ketogenesis at lower ratios of fat intake compared to combined carbohydrate and protein.

While animal models have suggested for many years that carbohydrate intake may increase the initiation and growth of cancers^[49,54,55], advancing technology now reveals numerous mechanisms by which manipulating cancer metabolism via carbohydrate restriction may impact outcome^[56-59]. One study demonstrated the potential of this strategy in which castrated mice fed a low carbohydrate diet showed a statistically significant reduction in prostate cancer tumor volume compared to mice fed a western diet^[60].

Ketosis may offer unique benefits in cancer prevention and prognosis above and beyond carbohydrate restriction. Ketosis induces many physiologic changes that can be leveraged for therapeutic benefit. The historic work at Johns Hopkins University pioneered the use of the ketogenic diet in the treatment of refractory pediatric epilepsy in the 1920's, with staggering results^[61]. The early work was validated in extensive clinical studies over the years, with systematic reviews and meta-analysis demonstrating the efficacy of the ketogenic diet for this condition^[62]. Currently, a number of ketogenic diet-based clinical trials are ongoing in several disease states, including adult epilepsy, metabolic syndrome, diabetes mellitus type II, Alzheimer's disease, and cancer.

Of particular relevance to cancer and the mechanisms described previously, the ketogenic diet reduces insulin resulting in downregulation of oncogenic signaling pathways, decreases circulating glucose leading to decreased tumor biomass production, and increases ketone

bodies with direct HDAC inhibition [38,47,63]. In light of these promising mechanisms, it is not surprising that the ketogenic diet has been shown to be efficacious as an adjuvant to numerous cancers in clinical studies, including ovarian, endometrial, pancreatic, and lung cancers [64,65]. While there are currently limited clinical studies evaluating outcomes of the ketogenic diet among prostate cancer patients, a recent review suggested that the anti-cachectic properties of ketones could be beneficial as adjuvant treatment [66]. The ketogenic diet is currently being evaluated for prostate cancer patients under active surveillance (NCT02194516).

Concerns over the high fat content of ketogenic diets are generally unwarranted, as systematic review and meta-analysis have shown that fat intake is not a risk factor for increasing incidence or lethality of prostate cancer [67]. Although a recent preclinical study examining the effects of a high fat diet in a mouse model of prostate cancer showed increased risk of metastases, [68] all the mice in the study gained weight and received 21% of their calories from carbohydrates. This value is significantly higher than the amount of carbohydrates permitted with ketogenic or low carbohydrate/modified Atkins interventions [69]. Moreover, in contrast to the weight gain experienced by mice with the high fat diet, human studies of low carbohydrate and ketogenic diets have uniformly led to weight loss, and have generally outperformed low fat diets in this regards [70]

Micronutrient Interventions

Dietary intake and circulating concentrations of lycopene, a red-pigmented carotenoid found in tomato and watermelon, have been associated with lower incidence and aggressiveness of prostate cancer. A recent systematic review and meta-analysis of several large observational studies [71] revealed a 12% reduction in risk with both intake and concentrations of lycopene, with a linear dose-response relationship between 1% reduction in risk for each 2mg of lycopene consumed. While lycopene interventions among prostate cancer patients are limited at present and have not been as encouraging [72], lycopene intake may benefit men at risk of prostate cancer due to the multiple complementary mechanisms through which this nutrient could play a role in cancer.

Lycopene possesses potent antioxidant properties, prevents DNA damage, inhibits tumor cell proliferation and growth, and mediates cell cycle arrest [73]. In addition, lycopene has been shown to inhibit IGF-1 signaling [74] and decrease cholesterol metabolism [75]. The LDL-lowering effects of lycopene have been confirmed in human clinical trials, including systematic review and meta-analysis [76] of lycopene interventions. It should be noted that the mechanism through which lycopene lowers LDL is distinct from statin medications, thereby providing another option for statin-intolerant patients. Interestingly, a recent study identified associations between variants of the SETD7 gene and serum lycopene concentrations after a standardized diet. Both lycopene concentrations and SETD7 have been independently associated with prostate cancer, suggesting potential interplay between diet, gene expression, and prostate cancer incidence and progression [77].

Limitations of Available Data

While animal models and clinical data demonstrating improved metabolic outcomes with low-carbohydrate and ketogenic diets are encouraging given the increasingly well-recognized role of metabolic contributors to prostate cancer, more clinical studies are required. Ongoing clinical trials ([NCT02194516](#), [NCT03679260](#)) among prostate cancer patients under active surveillance should provide more direct evidence regarding the benefits of low carbohydrate/ketogenic diets. Additional studies examining other forms of dietary intervention may provide complimentary data ([NCT00082732](#), [NCT01802346](#), and [NCT01238172](#)).

Similarly, while the evidence in systematic reviews and meta-analyses of both observational and clinical studies of lycopene are also highly encouraging, more clinical studies are required to conclusively understand the potential differences between lycopene, interventions with tomato products, and tomato products as a component of an otherwise healthy dietary pattern.

While the focus of this review has been on two dietary interventions with well-established metabolic impact, other diets and dietary components have demonstrated protective effects against prostate cancer. These strategies include, but are not limited to, the Mediterranean Diet [78], coffee (caffeinated and decaffeinated)[79], and green tea [80].

Conclusion and Future Directions

Prostate cancer remains a significant cause of global mortality. Available data suggests a strong association between metabolic syndrome factors and prostate cancer incidence and aggressiveness. Diabetes may have a reciprocal relationship with the risk of prostate cancer development, but certainly has a negative impact on disease progression. Additionally, metabolic syndrome may develop as a consequence of prostate cancer treatment with ADT, and may contribute to castration resistance and disease progression. Obesity is negatively associated with prostate cancer with recent data indicating that peri-prostatic adipocytes may secrete factors that promote extra-prostatic tumor progression. These associations suggest a strong need for the examination of dietary interventions in the overall treatment of prostate cancer. Low carbohydrate and ketogenic approaches may be favored given their mechanistic anti-tumor underpinnings and their superior impact in clinical trials. Attention should also be paid to micronutrient content of the diet in light of the epigenetic activity and HDAC inhibition noted with many micronutrients such as lycopene. Given preliminary data suggesting a link between variants of the SETD7 gene, lycopene concentrations and prostate cancer, future studies should consider the impact of genetics on variable responses to preventive and therapeutic dietary approaches in prostate cancer.

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* Studies of special interest.

** Studies of outstanding interest.

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Key Points

- Peri-prostatic adipocytes promote extracapsular extension of prostate cancer through chemokines, providing a mechanistic link between obesity and prostate cancer progression.
- Peri-prostatic fat tissue volume is predictive for response to androgen deprivation therapy.
- PI3K inhibitor resistance may be caused by hyperinsulinemia and potentially prevented with a concurrent ketogenic diet intervention.
- Lycopene influences prostate cancer through inhibition of IGF-1, with the effects modulated at the gene expression level.
- Low carbohydrate diet interventions may have a positive effect on prostate cancer through their impact on components of metabolic syndrome.