Capodice J, Cheetham P, Stewart R, Liaw B. Prostate Cancer and Obesity: Current Hypotheses and Challenges. *IJCCD*. Published online October 6, 2024.
doi:10.53876/001c.120988

Review Article

Prostate Cancer and Obesity: Current Hypotheses and Challenges

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Keywords: prostate cancer, obesity, adipokines, leptin, IGF1, periprostatic fat, weight loss

https://doi.org/10.53876/001c.120988

International Journal of Cancer Care and Delivery

Prostate cancer is the most common cancer diagnosed in males in the United States. Known prostate cancer risk factors include age, ethnicity, and genetic factors. There is some data suggesting that obesity is a risk factor for numerous aspects related to prostate cancer including prostate cancer development, biochemical recurrence, and prostate cancer mortality. Moreover, there may be potential therapeutic complications in the obese patient. Weight loss has also been shown to benefit the patient with prostate cancer. Finally, obesity may affect the microbiome and other molecular pathways such alterations in adipokine signaling, insulin and the insulin-like growth factor 1 pathway, and effects on the tumor microenvironment (e.g.: ectopic/periprostatic fat). The purpose of this review is to discuss the most current hypotheses on the relationship between obesity and prostate cancer across this broad spectrum of potential relationships.

Take Home Message

- Prostate cancer, the most common cancer in U.S. males, has risk factors including age, ethnicity, genetic factors, and potentially obesity.
- Obesity may influence various prostate cancer aspects, such as development, recurrence, mortality, therapeutic complications, and benefits from weight loss.
- Obesity could also impact the microbiome and molecular pathways, including adipokine signaling, insulin pathways, and the tumor microenvironment, with this review exploring these relationships.

1. INTRODUCTION

Worldwide, prostate cancer is the second most diagnosed cancer in men and in the United States (US), prostate cancer is the most common cancer diagnosis in males.[1,2] In 2022 the US the estimated number of prostate cancer cases and deaths were approximately 268,490 new cases and 34,500 deaths respectively.[2] There are several known prostate cancer risk factors including age, ethnicity, family history and genetic factors and there is a strong possibility that obesity is a risk factor for prostate cancer development. There are numerous studies that have demonstrated statistically significant associations between obesity and total prostate cancer incidence, advanced prostate cancer, and as a prognostic factor for prostate cancer outcomes such as biochemical recurrence. However, there are also conflicting studies suggesting the opposite.[3,4]

Obesity also can cause considerable therapeutic challenges in surgical, radiation therapy, and short- or long-term androgen deprivation therapy. Obesity is a modifiable risk factor and studies on physical activity and weight loss predominately through lifestyle interventions have also been shown to confer benefit in prostate cancer patients at various phases in treatment.

The most current hypotheses and potential mechanisms of action of the relationship between prostate cancer and obesity include alterations in adipokine signaling, insulin and the insulin growth factor-1 (IGF-1) pathway, and the tumor microenvironment and periprostatic fat (Figure 1). Targeted obesity treatments which might affect treatment outcomes include adipokine and IGF-1 targeted drugs, weight loss and physical activity, and newer drugs such as glucagon-like peptide-1 receptor agonists (GLP-1 agonists). The literature review for this paper was first conducted via a search of the PubMed and OVID/Medline databases using the keywords ‘prostate cancer’ and the following terms: 'obesity, ‘adipokines’, ‘leptin’, ‘IGF-1’, ‘interstitial growth factor-1’, ‘weight loss’, ‘periprostatic fat’, ‘tumor microenvironment’, ‘physical activity’, ‘biochemical recurrence’, ‘mortality’, ‘surgical complications’, ‘radiotherapy complications’, ‘prostate microbiome’, ‘androgen deprivation therapy’. We reviewed full-text, accessible articles in the English language published in the last twenty years. Two reviewers (JLC and PC) independently evaluated the potentially relevant studies for inclusion in the discussion. This paper hopes to provide the clinician and researcher with a timely review of this important topic.

2. OBESITY AS A RISK FACTOR FOR PROSTATE CANCER DEVELOPMENT

It has recently been shown that obesity is a risk factor for the development of at least twelve types of cancer includ-

ing colorectal, endometrial, and renal cancers.[5] Obesity has been shown to be a risk factor for advanced prostate cancer, prostate cancer mortality, and biochemical recurrence but the relationship between risk of total prostate cancer incidence and obesity is still inconclusive.[5,6] Obesity is clinically measured by the metric body mass index (BMI). Body mass index is defined as the ratio between height and weight. A body mass index between the range of 18.5 to 24.9 kg/m^2 BMI is categorized as normal, 25-29.9 kg/m^2 BMI is overweight, and > 30 kg/m^2 BMI is considered obese. There are known limitations regarding BMI as a health index as BMI is not directly related other health parameters and it is non-specific in that it does not give any information about lean versus fat mass or adipose tissue location throughout the body (7 added new reference).

In developed countries more than 70% of adults have been shown to be either overweight or obese.[7] Obesity is also associated with incidence of heart disease, stroke, and diabetes mellitus.[7] Obesity is implicated as a disruptor of several metabolic and endocrine pathways and disruptions in these pathways are thought to adversely affect cancer cell metabolism.[8] The molecular pathways implicated cause aberrant molecular signaling which may drive prostate cancer incidence, progression, and biochemical recurrence.[9-12]

2A. OBESITY AS A PROGNOSTIC FACTOR FOR ADVANCED PROSTATE CANCER, BIOCHEMICAL RECURRENCE AND PROSTATE CANCER MORTALITY

Obesity has been shown to be associated with an increased risk of prostate cancer mortality, advanced prostate cancer, and biochemical recurrence.[3] A meta-analysis of six population-based cohort studies following men for an average of more than 10 years demonstrated a 15% higher risk of death from prostate cancer (RR 1.15, 95% CI: 01.06–1.25) with each 5 kg/m^2 increase in BMI.[8] The same metanalysis demonstrated a 20% increased risk of prostate cancer–specific mortality in post-diagnosis patients (RR: 1.20, 95% CI: 0.99–1.46, P = 0.06) associated with each 5 kg/m^2 increase in BMI.[8] A recent study by Perez-Cornago et al demonstrated in a metanalysis of prospective studies including 19,633 patients, prostate cancer deaths for BMI, 670 for body fat percentage, 3181 for waist circumference and 1639 for waist to hip ratio, of men who died from prostate cancer. The combined hazard rations (HRs) for dying from prostate cancer for the increments above were 1.10 (1.07-1.12), 1.03 (0.96-1.11), 1.07 (1.03-1.11), and 1.06 (1.01-1.10), respectively.[13]

Studies that link obesity and advanced prostate cancer include a few studies that have examined waist circumference and advanced prostate cancer risk. A study of 150,000 European men demonstrated that larger waist circumference was associated with risk of advanced prostate cancer[14] while the Health Professionals follow up study did not show any association between waist circumference and advanced prostate cancer.[14,15] Prospective studies have also demonstrated that increased physical activity might be protective and reduce advanced prostate cancer risk. Men over the age of 65 who were classified as vigorously active demonstrated a 77% lower risk of developing advanced prostate cancer over a 14-year follow up period while a more recent meta-analysis showed no association between overall physical activity and advanced or aggressive prostate cancer.[15-17] A more recent meta-analysis also showed that a higher pre-diagnosis BMI, but not post-diagnosis BMI was associated with increased risk of death from prostate cancer (HR=1.15, 95% CI: 1.07–1.23, P<0.01).[18]

Obesity has been demonstrated to increase the risk of biochemical recurrence in men with prostate cancer. In the abovementioned study by Cao et al, a meta-analysis of 16 studies investigated the relationship between BMI and biochemical recurrence in 26,479 prostate cancer patients that were followed over a 2–10-year period. Results demonstrated that a 5 kg/m^2 increase in BMI was associated with a 21% increased risk of biochemical recurrence (RR: 1.21, 95% CI: 1.11–1.31, P < 0.01).[8] Other studies have further analyzed the relationship between BCR and prostate cancer. The most recent metanalysis demonstrates that increased BMI is associated with BCR (HR: 1.25, 95% CI: 1.11-1.39, I^2: 70.3%), and there was a 10% increase (95% CI: 4-15%, I^2: 66.3%) in BCR per 5 kg/m^2 increase in BMI, however there is a high level of heterogeneity in the trials and there is no consistent definition of BCR across studies, for example BCR was measured by prostate specific antigen (PSA) levels over a predefined threshold and there were different definitions based on therapy (e.g.: radiation or surgery).[19]

It is also important to note that there are conflicting studies suggesting that obesity may be protective in prostate cancer. An analysis by Xu et al, showed that men with non-metastatic castrate- resistant prostate cancer with a high BMI had a minor reduced risk of all-cause mortality ((HR 0.98, 95 % CI 0.97–0.99)[20] and a similar association between reduced prostate cancer-specific mortality was shown in another recent study of men with metastatic castrate resistant prostate cancer (mCRPC).[21] A recent meta-analysis analyzed studies measuring differences in lean fat mass with overall survival (OS) in men with prostate cancer. This study demonstrated that total adiposity was not significantly associated with OS (hazard ratio (HR) 0.98, 95% CI: 0.75–1.28, p = 0.888) or visceral adipose tissue (VAT) composition.[22] This study also showed that men with lower muscle mass levels compared to those presenting with high muscle mass levels had a greater mortality risk of both localized and advanced disease (localized (HR 1.91, 95% CI: 1.40-2.62, p < 0.001) and advanced disease (HR 1.43, 95% CI: 1.07-1.92, p = 0.020)).[21] Fifteen of sixteen of the studies utilized computed tomography (CT) scans for fat and muscle mass assessment and it has been suggested that there are metabolic differences between subcutaneous versus visceral fat levels.[22,23] A considerable challenge remains in fleshing out the mechanisms of action linking obesity and prostate cancer incidence and section 5 of the review focuses on some of the molecular pathways that are thought to be influenced by obesity.

3. OBESITY AND THERAPEUTIC COMPLICATIONS IN PROSTATE CANCER

Patients with higher BMI might also be at risk for therapeutic complications in prostate cancer. Radiation therapy is a commonly used modality in the treatment of prostate cancer. Studies have shown inferior biochemical control in men with elevated BMI following definitive radiotherapy.[24, 25] This may be in part due to worsened biology of prostate cancer seen in obese men, however technical aspects of radiation may also play a role. Increased body adiposity poses some challenges for radiation delivery. Daily patient setup is based on alignment of preplaced skin tattoos with wall mounted lasers. High volume abdominal fat results in daily variation in body surface contour and thus the daily positioning of the skin tattoos. This body surface mobility increases potential for setup error. A study performed by Wong demonstrates that obese patients require larger corrective shifts compared to lower BMI cohorts.[26] The variation in daily body contour can alter the deposition of radiation in the body, making dose distribution unpredictable. This necessitates the need for techniques to manage and monitor the surface anatomy to ensure daily reproducibility. Image guidance refers to radiographic localization and targeting of the prostate prior to treatment. This is now standard practice in prostate radiation, bypassing some setup limitations. However, the quality of radiology such as kilovoltage and cone beam computed tomography imaging deteriorates with obesity and is subject to artefact.[27] This renders prostate identification and targeting more challenging and increases the risk for partial treatment misses. An additional complication factor is that CT simulators and linear accelerators are constrained by weight and bore diameter limits. Equipment with higher weight tolerances and larger bore diameters are on the market, however, are not readily available at many treatment centers. Those who do not meet these physical limits are effectively unable to undergo radiotherapy therefore weight loss strategies for the obese patient are important in the curative aspect of prostate cancer treatment.

Surgical treatment of prostate cancer includes radical prostatectomy which is most performed as robot assisted radical prostatectomy (RARP) in the US. Obesity and prostate cancer complications in surgery include risks related to surgical candidacy of the patient including cardiovascular and anesthesia risks such as the American Association of Anesthesiologists' (ASA) score.[28] For example, an analysis of 211 consecutive patients undergoing RARP showed that high BMI increased the risk of high-grade complications (odds ratio, OR 1.184; P = 0.047).[29]

Cardiometabolic health, risks, and prostate cancer treatment are also considerable concerns in men with prostate cancer. A recent single-center analysis demonstrated that men with prostate cancer undergoing androgen deprivation therapy (ADT) had high metabolic risk and in the sample of 55 men, 93% were overweight or obese and 84% of men had an overlap of two or more cardiometabolic diseases.[30] It is also well known that long-term ADT increases cardiometabolic risk and morbidity in men with prostate cancer.[31] A recent small single center study showed that a comprehensive lifestyle program improved numerous health metrics including weight, waist circumference, systolic and diastolic blood pressure, and serum triglycerides (P<0.001, P<0.001, P=0.014, P=0.0056, P=0.022) respectively.[32]

4. WEIGHTLOSS AND PROSTATE CANCER

A few studies have evaluated the impact of weight loss on prostate cancer tumor traits and biomarkers in men with prostate cancer. A single-blind presurgical randomized controlled trial of 40 overweight or obese men with newly diagnosed prostate cancer, 67.5% were Gleason Grade Group 2 or less and 32.5% were Gleason Grade Group 3 or higher, assessed feasibility, changes in serum biomarkers, tumor markers, and lymphocytic gene expression after a weight loss intervention. The weight loss intervention was comprised of caloric restriction, increased physical activity, and behavioral modifications. Results demonstrated that lean and fat mass decreased in both the treatment group and the control group, testosterone and sex hormone binding globulin increased in the weight loss versus control group (P=0.0418 and 0.0023), and leptin was decreased in the weight loss versus the control group respectively (p=0.0355). There were no significant changes in other serum biomarkers including VEGF, TNF-b, insulin, glucose, and PSA.[33] The weight loss group also demonstrated significantly greater Ki67 proliferation rates in tissue post-prostatectomy as well as changes in several gene expression panels.[33] These results were confounding as the hypothesis was that tumor proliferation would decrease with weight loss. In a follow up analysis to this study the authors demonstrated that there were positive associations between change in percentage of body fat and free fatty acids ($\rho = 0.428$, $p = 0.026$). They also demonstrated that change in Ki67 was inversely associated with change in lean mass ($\rho = -0.912$, $p = 0.001$) and change in insulin ($\rho = -0.650$, $p = 0.042$). The authors suggest that these results may be due to differences in metabolic regulation following degradation of lean body mass and suggest that resistance training might be important along with fat loss to exert desirable changes in biomarkers and gene expression.[34] Other weight loss studies have been performed suggesting that weight loss may improve surgical and clinical outcomes such as decreasing adverse events and improving lean mass and blood pressure.[35] The American Society of Cancer Oncologists (ASCO) recently published a guideline for cancer patients based on clinical studies and found that exercise improved cardiorespiratory fitness and body composition and weight in prostate cancer patients on ADT.[36] Finally, as abovementioned, weight loss studies in men with advanced prostate cancer have shown numerous improved cardiometabolic health status.[31]

5. MECHANISMS OF OBESITY AND PROSTATE CANCER

5.1. ADIPOKINE INTERPLAY: LEPTIN AND ADIPONECTIN

Adipose tissue has been recently characterized as an endocrine organ that is capable of secreting bioactive peptides commonly called adipokines. Adipokines are cell signaling molecules that can become dysregulated in a chronic inflammatory state and may result in deleterious effects on various target tissues throughout the body.[23,37] Letpin and adiponectin are the two most commonly studied adipokines but there are numerous adipokines in the body. Leptin is produced in both adipose and non-adipose tissue and acts to regulate appetite and energy expenditure. It circulates in the bloodstream in a free and leptin-receptor bound state and plasma leptin levels are proportional to both fat mass and body weight.[23,37] Leptin has been found to be associated with a protumor effect in prostate cancer cell lines causing increased proliferation, decreased apoptosis, increased cell migration, and alterations in the STAT3 pathway.[38] Elevated leptin levels have also been shown to be increased in prostate cancer patients with higher volume disease and leptin receptor mutation has also been associated with increased risk of prostate cancer.[39,40] Leptin receptor antagonists are in development and have been tested on breast and prostate cancer cell lines and have demonstrated inhibition in prostate cancer xenograph models.[41,42]

On the other hand, adiponectin is an adipokine that may have an antitumor effect. Adiponectin helps to regulate inflammation, lipid and glucose metabolism, and sensitizes insulin. Adiponectin dysregulation has been recently shown to be associated with the progression of obesity-related cancers including breast, colorectal, liver, ovarian, pancreas, and prostate cancers and low adiponectin levels are also associated with metabolic syndrome, diabetes mellitus, insulin resistance, hypertension, and cardiovascular disease.[43] The feedback mechanism of adiponectin loss in the obese state is still yet to be understood but increased levels of leptin and inflammatory cytokines such as interleukin 6 (IL-6) and Tumor necrosis factor-alpha (TNF-a) have been shown to inhibit adiponectin transcription.[43,44] In molecular studies of adiponectin and prostate cancer, adiponectin has been shown to inhibit vascular endothelial growth factor (VEGF) and may suppress prostate cancer cell growth through AMP-activated protein kinase (AMPK) activation and subsequent inhibition of mammalian target of rapamycin (mTOR).[45,46] A recent meta-analysis of 2,504 patients versus 3,565 controls demonstrated that patients with prostate cancer versus controls had lower serum adiponectin levels (95% CI, -1.345 to -0.440, p=0.000).[46] Other studies have found weak associations between circulating adiponectin levels and prostate cancer risk.[47] Finally, a recent study of a new adiponectin receptor agonist demonstrated significant growth inhibition in a LNCaP xenograph model.[48]

5.2. INSULIN AND THE INSULIN GROWTH FACTOR-1 PATHWAY AND PROSTATE CANCER

It was originally suggested that increased levels of circulating insulin (hyperinsulinemia) may contribute to the development of cancer.[49,50] The hypothesis is that increased levels of circulating insulin may affect various aspects of the insulin-like growth factor (IGF) axis, in particular the insulin growth factor 1 (IGF-1) pathway. In a hyperinsulinemic state prolonged levels of increased insulin have been shown to affect IGF-binding proteins 1- and 2 by reducing their production which in turn may promote a tumor cell microenvironment.[51] Cancer cells thus may be able to survive better because of increased IGF signaling which is also thought to induce angiogenesis in tumors.[37,52] Many basic science studies have demonstrated the role of the IGF axis in prostate cancer. Increased IGF-1 signaling has been shown to be elevated in prostate cancer tissue versus benign prostatic tissue.[53-55] Epidemiologic studies have also shown that increased serum IGF1 levels may be associated with increased risk for prostate cancer development.[56,57]

5.3. PROSTATE CANCER AND GUT MICROBIOME

A recent area of interest regarding obesity, weight loss, and prostate cancer includes potential changes in the gut microbiome in patients with prostate cancer. The first factor related to cancer and the microbiome is called dysbiosis. This term refers to a dysregulation in the microbiome that might be related to a disease process. The main hypothesis linking the microbiome to a pathologic condition is the example of the involvement of infection in the development of cancer such as the case of human papilloma virus (HPBV).[58,59] However, there are more complex and less understood hypotheses on how dysbiosis leads to cancer. In prostate cancer there are several factors that might be at play, first the presence of prostate microflora and any dysregulation might be related to prostate cancer tumorigenesis. Second the genitourinary and gut microbiomes which includes changes in the urinary microbiome and gastrointestinal microbiome might also be related to prostate cancer although no specific organisms have been identified. For example, a recent study analyzed the relationship between weight loss, dietary changes, the gut microbiome, and Gleason scores prior to radical prostatectomy.[60,61] This study compared fecal microbiota of newly diagnosed, treatment-naïve, overweight and obese cancer patients and matched controls and demonstrated that prostate cancer patients had higher Chao1 (p=0.006) and Observed Species (p=0.036) than cancer-free males. Various bacteria in the order Clostridiales were also different in men with prostate cancer versus controls.[60] A recent basic science study analyzed prostate specimens obtained by radical prostatectomy to identify potential microbiota and/or pathogens thought to be associated with prostate cancer. Results demonstrated that four bacteria including Moraxella osloensis, Uncultured chroococcidiopsis, Cutibacterium acnes, and Micrococcus luteus were found as possible pathogens.[62] The authors further went on to analyzes whether C. acnes affected gene expression in prostate cells and found changes in sev-

eral molecular pathways.[62] These data are difficult to interpret at this time as there is a lot of research that needs to be done to examine how differences in microbial patterns are related to cancer risk and disease. Nevertheless, this suggests another possible relationship between obesity, the tumor microenvironment, and prostate cancer.

5.4. THE TUMOR MICROENVIRONMENT AND PERIPROSTATIC FAT

Other hypotheses about the relationship between prostate cancer and obesity include the tumor microenvironment as it relates to ectopic fat.[63-65] Ectopic fat is defined as excess adipose tissue in an area not typically associated with adipose tissue storage and an important example in prostate cancer is periprostatic adipose tissue or fat (PPAT).[64,66,67] Periprostatic adipose tissue (PPAT) is located in the subperitoneal area and delineated by the anterior pubic symphysis, lateral obturator muscles, and posterior recto-prostatic fascia.[68,69] There are numerous reference standards and imaging methods of PPAT including magnetic resonance imaging, computed tomography, and transrectal ultrasound however it has been shown in numerous studies that the ectopic fat microenvironment is responsible for secreting additional proteins, cytokines, and adipokines locally which may enhance the proliferation of prostate cancer cells and/or tumor aggressiveness and may also be correlated with increased periprostatic fat volume.[64,66]

The hypothesis suggesting that periprostatic fat is a metabolically active part of the tumor microenvironment is relatively new. One of the early studies analyzed whether periprostatic fat density contributed to changes in serum cytokine levels or correlated with pathologic tumor grade in men scheduled to undergo radical prostatectomy. The investigators found that higher IL-6 levels in PPAT medium correlated with increased Gleason grade.[70] Subsequent studies analyzed PPAT and prostate cancer aggressiveness. Van Roermund et al measured PPAT in patients undergoing brachytherapy for localized disease and found no association between fat measurement and high-risk disease however there was a strong association between high BMI and higher levels of subcutaneous PPAT.[69,71] A recent clinical study also showed a significant association (Odds ratio [95% CI] 1.06 [1.04–1.08], P< 0.001) between periprostatic fat density (PFD) and high-risk disease (PSA > 20 or Gleason score ⩾8 or T3).[72] Magnetic resonance imaging and TRUS analysis of PPAT and correlation with aggressive disease has also been shown.[73,74] Finally basic science studies utilizing PPAT conditioned media also demonstrate oncogenic changes in the tumor microenvironment including altered gene expression in molecules involving cell proliferation, anti-apoptosis, adipogenic, and immunoinflammatory processes.[75,76]

6. NOVEL TARGETS IN PROSTATE CANCER AND OBESITY

Several therapeutic strategies for inhibiting the IGF-1/IGF-1R pathway have been in development. Clinical trial experience with anti-IGF-1R monoclonal antibodies, designed to prevent ligand-receptor interaction and downstream signal activation, has been mixed. A randomized phase II study of cixutumumab, an anti-IGF-1R recombinant human IgG1 monoclonal antibody, in combination with androgen deprivation therapy (ADT) vs. ADT alone in metastatic hormone sensitive prostate cancer showed a trend towards improvement in the undetectable prostate specific antigen (PSA) rate which was 42 (40.0%) of 105 for those receiving ADT plus cixutumumab and 34 (32.3%) of 105 for those receiving ADT alone (RR, 1.24; one-sided P = .16). The addition of cixitumumab was not associated with IGF-1R biomarker changes and did not confer an overall survival benefit.[77,78] In a phase II study that randomized men with mCRPC to receive either figitumumab, a human IgG2 monoclonal antibody, with docetaxel vs. docetaxel alone the primary endpoint of PSA response was not met, and the combination arm experienced substantially more toxicity as compared with docetaxel alone.[79] However, in the group of patients that crossed-over and had figitumumab subsequently added following progression on docetaxel, there was a notable PSA response of 28%, suggesting that there is activity to IGF-1R inhibition in the right clinical scenario.[79] IGF-neutralizing monoclonal antibodies that target ligands IGF-1 and IGF-2 have been evaluated in preclinical and early phase studies,[80-84] although not yet in prostate cancer dedicated studies. Experience with IGF-1R small molecule tyrosine kinase inhibitors have primarily been in preclinical studies,[85,86] except for a phase II single arm study of linsitinib in mCRPC, which was terminated early as it failed to show a significant objective and PSA response.[87]

With the recent approval and increased use of medical therapy for weight loss including opiate antagonist, lipase inhibitors, and glucagon-like peptide 1 agonists, as well as surgical management for obesity prior to oncologic treatment, the relationship of weight loss on prostate cancer development, prognostic factors, and the potential of these therapies to assist lifestyle interventions and possibly reduce therapeutic complications is promising.

7. CONCLUSION

Obesity is prevalent in society and might be a risk factor for the development, progression, and prostate cancer mortality. Curative and long-term management of prostate cancer in the obese patient also presents a variety of challenges. Obesity is a modifiable risk factor and weight loss via lifestyle interventions including diet and physical activity, medical, or surgical treatment can impact prostate cancer management. The basic science and clinical evidence suggesting the relationship between obesity and prostate cancer includes alterations in adipokine signaling, the IGF-1 pathway, dysbiosis, and changes in the tumor microenvironment. There are novel targets related to these various pathways that are promising new treatment strategies for both reducing obesity and other related oncologic and systemic health risks.

CONFLICT OF INTEREST

None

FUNDING INFORMATION

N/A

ETHICAL STATEMENTS

N/A

ACKNOWLEDGEMENT

N/A

AUTHOR CONTRIBUTIONS

I. conception and design: Jillian L Capodice
II. data collection and assembly: All authors
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All authors have approved this manuscript.

Submitted: February 28, 2024 PDT, Accepted: June 29, 2024 PDT

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SUPPLEMENTARY MATERIALS

Figure. Changed

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