Review – Prostate Cancer

Obesity and Prostate Cancer: A Role for Adipokines

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Abstract

Objectives: Many studies have investigated the association between obesity and prostate cancer risk but have yielded inconsistent results. Recent evidence suggests a particular role for obesity in prostate cancer progression. Many studies have investigated the roles of adipose tissue-derived factors (adipokines) as putative molecular mediators between obesity and prostate cancer. This review provides an overview of current evidence that supports such a role for adipokines.

Methods: A comprehensive literature review was carried out using PubMed to search for articles relating to prostate cancer and the following adipokines: leptin, interleukin 6, vascular endothelial growth factor (VEGF), and adiponectin.

Results: Prostate cancer cells are exposed to adipokines either via the circulation or through locally produced adipokines following invasion of the retropubic fat pad. Circulating levels of most adipokines are positively correlated with obesity; adiponectin is inversely correlated with obesity. High circulating levels of leptin, interleukin 6, and VEGF are associated with increased prostate cancer risk and increased aggressiveness. Adiponectin levels are lower in patients with prostate cancer and are inversely associated with grade of disease. Adipokines exert a variety of biologic effects on prostate cancer cells, modulating cellular differentiation, apoptosis, proliferation, and angiogenesis.

Conclusions: Evidence suggests a role for obesity and adipokines in promoting the progression of established prostate cancer. Adipokines may contribute to the molecular basis for the association between obesity and prostate cancer, but the complex pathophysiology of both these disease states requires further studies.

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1. Introduction

Prostate cancer is one of the most commonly diagnosed malignancies in men and the second leading cause of cancer-related death worldwide. In Europe 2.6 million new cases are diagnosed each year and prostate cancer accounts for 9% of all cancer deaths among men within the European Union [1]. The incidence and disease-specific mortality of prostate cancer demonstrate marked geographic variation, being greatest in North America and western European countries. Even within Europe, there is a notable difference between northern and southern countries, with prostate cancer incidence and mortality being highest in England and Wales and lowest in Mediterranean countries such as Spain, Italy, and Portugal [2]. Worldwide, the lowest incidence of prostate cancer is in Asian men, but recent studies have shown that rates have risen rapidly in the past two decades in most Asian countries [3]. Furthermore, the differences in prostate cancer incidence between the indigenous American population and Asian immigrants are reducing, reflecting a potential influence of environmental risk factors on Asian immigrants [3]. However, the possibility that these changes may partly be attributable to recent improvements in diagnostic methods cannot be excluded. Differences in prostate cancer incidence among ethnic populations undoubtedly have a genetic component, but the contribution of environmental factors in the pathogenesis of this disease, in particular the influence of diet and the “Western lifestyle,” is gaining recognition.

Obesity is reaching epidemic proportions in Western populations and is commonly attributed to the high fat consumption and the sedentary lifestyles of Western populations. It is a significant public health concern, being linked with diseases such as type 2 diabetes and cardiovascular disease. Visceral (central) obesity, in particular, is associated with insulin resistance, hyperglycaemia, hyperinsulinaemia, dyslipidaemia, hypertension, and prothrombotic and proinflammatory states [4]. The term “metabolic syndrome” encompasses these biochemical abnormalities and clinical conditions that may or may not be associated with central obesity.

Thus, a geographic correlation exists between areas of high prostate cancer and obesity incidence. Numerous studies have been performed to examine the association between obesity and prostate cancer, but they have yielded inconsistent results [5]. This may, in part, be due varying methods of anthropometric measurement, such as body mass index (BMI) and the waist-to-hip ratio (WHR). However, a recent study has shown visceral fat accumulation, as quantified by computed tomography (CT), is a specific risk factor for prostate cancer [6]. More consistent results have been obtained with studies looking at obesity and progression of prostate cancer. Indeed, it has recently been suggested that obesity may reduce the risk of nonaggressive disease while concurrently increasing the risk of aggressive disease [5]. Therefore, it is possible that rather than increasing the absolute risk of prostate cancer development, obesity may be associated with the progression of latent or microscopic prostate cancer to clinically significant and metastatic prostate cancer.

The importance of testosterone/androgens in prostate growth is well accepted; however, androgens demonstrate a complex interaction with obesity. There is a well-documented age-related decline in serum testosterone, with obesity itself also resulting in decreased free testosterone in men [7]. Data from retrospective studies suggest that testosterone may exert a differentiating effect on prostate cancer; decreased serum testosterone levels have also been associated with more advanced and poorly differentiated tumours at presentation [8,9]. Thus, obesity may compound physiologic age-related hypoandrogenaemia in men and consequently provide an environment whereby aggressive, partially androgen-insensitive prostate cancers can thrive [10]. Additionally, increased peripheral aromatisation of androgens to oestrogen in adipose tissue, which is related to the degree of adiposity, also contributes to a decline in serum androgen levels. Conversely, hyperinsulinaemia, which is a feature of the metabolic syndrome and obesity, has been shown to up-regulate testosterone production [7]. This same study also demonstrated a reduction in hepatic sex hormone-binding globulin (SHBG) production, which would result in higher levels of free bioactive androgen [7].

One of the most marked characteristics of the Western diet is a high calorie and saturated fat intake. Although there are no conclusive studies showing an association between total dietary fat intake and prostate cancer risk, specific types of dietary fat (eg, animal fat) appear to be more significant in increasing prostate cancer risk [11,12]. The most abundantly consumed fatty acid in the Western diet is linoleic acid (omega-6 polyunsaturated fatty acid), which has recently been shown to promote prostate cancer migration in vitro [13]. In vitro studies have also shown that high levels of saturated fat act as a growth factor in a variety of prostate cancer cell lines, whereas a
low-fat diet results in slower androgen-sensitive prostate cancer growth and can delay progression [14,15]. Furthermore, results from a recent large prospective study found that use of cholesterol-lowering statin drugs was associated with a reduced risk of advanced (especially metastatic or fatal) prostate cancer [16].

The molecular mechanisms underlying the association between obesity and prostate cancer are numerous and occur at many levels. As well as altering circulating androgen levels, obesity also affects other hormones such as insulin-like growth factors (IGFs), which are known to have mitogenic properties. Oestrogen levels are also elevated due to their conversion from androgens in adipose tissue. It is therefore not surprising that obesity has also been associated as a risk factor for many cancers, in particular, hormone-dependent cancers such as breast, endometrial, and prostate cancer. It has also been shown that prostate cancer cells cultured in the presence of fat cells (adipocytes) demonstrate altered proliferation, differentiation growth, and cytokine expression, suggesting that adipocyte-derived factors may modulate the biologic behaviour of prostate cancer cells [17].

Obesity results from an accumulation of white adipose tissue (WAT), which is a metabolically active endocrine organ, as opposed to a mere repository for excess energy [4]. Adipocytes secrete a variety of hormones, bioactive peptides, and cytokines, termed adipokines, such as leptin, adiponectin, and vascular endothelial growth factor (VEGF). Moreover, many of the aforementioned adipokines have been shown to differentially modulate cellular differentiation, apoptosis, proliferation, and angiogenesis. In addition to adipocytes, adipose tissue also consists of connective tissue matrix, nerve tissue, vascular cells, and immune cells, which also secrete adipokines such as VEGF and tumour necrosis factor α (TNF-α). Adipokines may exert their biologic effects either at a local level via autocrine/paracrine pathways or in an endocrine fashion by entering the circulation and activating receptors on target cells. Paracrine effects of adipokines are important in cases of prostate cancer progression where extracapsular extension and invasion of the retropubic fat pad occurs. This could result in the exposure of malignant cells to high concentrations of potentially proangiogenic and proliferative factors, which may enhance further their capacity for further growth and metastasis [18].

Clearly, numerous mechanisms could contribute to the molecular association between obesity and prostate cancer, as summarised in Fig. 1. This review article provides an overview of the current evidence that supports a role for adipose tissue-derived

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**Fig. 1 – Diagrammatic representation of some of the possible mechanisms for obesity-related prostate cancer progression.**

IGF-1 = insulin-like growth factor 1; IL-6 = interleukin 6; VEGF = vascular endothelial growth factor; SHBG = sex-hormone binding globulin.
adipokines in the association between obesity and prostate cancer. It is not within the scope of this article to provide details on molecular mechanisms or to summarise epidemiologic evidence on this subject. We have focused our review on four of the major adipokines (leptin, interleukin 6 [IL-6], VEGF, and adiponectin) and have aimed to keep this review specific to their role as molecular mediators of obesity and prostate cancer, rather than carcinogenesis in general.

2. Materials and methods

We performed a PubMed literature search for articles from 1990 to 2006, with the search limited to articles in the English language. The search terms used included “adipokines,” “leptin,” “interleukin 6,” “vascular endothelial growth factor,” and “adiponectin,” linked with “and prostate cancer.” Articles were reviewed and those deemed relevant to this discussion were considered for this review. Articles were also identified from references cited in relevant articles, where appropriate.

3. Results

3.1. Leptin

Leptin, first described by Zhang et al in 1994 [19], is a 16-kD adipokine produced predominantly by adipocytes in WAT. Circulating leptin concentrations exhibit a positive correlation with total body fat, so that serum leptin is elevated in obese individuals compared to lean individuals [20]. Besides playing roles in the regulation of energy homeostasis, neuroendocrine physiology, and immune function, it is also speculated to be important in the development and maintenance of reproductive tissues, including the prostate [21].

Numerous studies have investigated the relationship between obesity, circulating leptin levels, and prostate cancer. A positive association between high leptin levels (after adjustment for BMI and serum testosterone) and the risk of large-volume prostatic tumours has been demonstrated [22]. A nested case-referent study by Stattin et al demonstrated an association between moderately elevated leptin concentrations and later development of prostate cancer [23]. It has also been shown that the association of leptin with prostate cancer risk is confined to men with a WHR > 0.87, suggesting the interaction of leptin with other markers related to abdominal obesity, such sex hormone bioavailability and IGF-1 levels [24]. Another group reported that serum leptin levels are correlated with prostate-specific antigen (PSA) and Gleason score in patients with prostate cancer, although the number of such patients included in this study was relatively small [25].

In vitro studies lend weight to support a putative role for leptin in prostate carcinogenesis. Onuma et al showed that leptin promoted the proliferation of androgen-independent prostate cancer cell lines [18]. Leptin has also been shown to promote vascular endothelial cell proliferation in vitro and angiogenesis in vivo, processes that are crucial to allow cancer progression, invasion, and metastasis. The study by Frankenberry et al also showed this increase in leptin-induced growth factor secretion was associated with an increase in prostate cancer cell migration, a feature of metastasis and angiogenesis [26].

The proliferative response of prostate cancer cells to leptin has been shown to involve intracellular signalling molecules such as phosphatidylinositol 3-kinase (PI3-K) and c-Jun NH2-terminal kinase (JNK) [18,27]. Alterations in these signalling pathways are not only critical in processes of prostate carcinogenesis and malignant transformation, but also important in obesity, diabetes, and insulin resistance [28].

3.2. IL-6

IL-6 is an adipokine that circulates at high levels, with serum concentrations being directly proportional to (visceral) obesity and insulin resistance [4]. Although not exclusively secreted by adipocytes, as much as one third of circulating IL-6 originates from adipose tissue, and expression and secretion of IL-6 are two to three times greater in visceral relative to subcutaneous adipose tissue [28]. It is implicated in the modulation of immune function and the regulation of a variety of cellular functions including proliferation, apoptosis, angiogenesis, and differentiation [29].

Serum IL-6 levels >7 pg/ml are associated with a poor prognosis in men with prostate cancer [30]. In addition, levels of IL-6 increase in organ-confined tumours, suggesting a role for IL-6 in the early stages of prostate carcinogenesis [31]. In vitro studies using androgen-independent prostate cancer cell lines show they secrete high levels of IL-6 into the culture medium [32], suggesting a function for IL-6 as an autocrine or paracrine regulator of prostate cancer growth (see Culig et al [29] for a comprehensive review). Obesity-related increases in IL-6 levels could thus potentially interfere and enhance this mechanism and further promote prostate carcinogenesis.

Hobisch et al developed a LNCaP subline, termed LNCaP-IL-6+, by treating LNCaP cells continuously...
with IL-6, and found that these cells displayed a higher basal proliferation rate and did not show growth inhibition in response to exogenous IL-6 [33]. In theory, this model could represent the chronic exposure of prostate cancer cells to high levels of IL-6 as occurs in obese patients in vivo. This transition of IL-6 from a growth inhibitor to a growth stimulator under such conditions could represent a mechanism whereby obesity results in an increased risk of prostate cancer progression.

### 3.3. VEGF

Serum concentrations of the adipokine VEGF are reported to be positively correlated with visceral fat mass [34]. VEGF is a potent mitogen, capable of stimulating cell migration, angiogenesis, and microvascular permeability [35]. As a key regulator of angiogenesis, VEGF plays a crucial role in the vascularisation of solid tumours such as those of the prostate, and thus facilitates local invasion of malignant cells and the development of distant metastases. However, in addition to its role as an angiogenic growth factor, it is now also apparent that VEGF also exerts direct growth factor effects on many tumourigenic cells, including the prostate [36].

Increased plasma VEGF levels have been reported in patients with metastatic prostate cancer compared to those with localised disease and healthy controls [37], although this study did not take into account differences in body mass or obesity. Plasma VEGF levels have also shown positive correlation with tumour stage, grade, and clinical outcome in men with prostate cancer [37].

Aggressive, high-grade human prostate cancers have shown high VEGF expression [38]. More interestingly, VEGF expression is increased in advanced prostate cancer where extension beyond the prostatic capsule, and into retropubic adipose tissue, has occurred [38]. Numerous studies have investigated the importance of VEGF in prostate carcinogenesis, but few have specifically addressed the role that VEGF may play in the context of obesity-related prostate carcinogenesis; Baillargeon et al provide a useful review [39]. VEGF plays a crucial role in prostate cancer progression, and it is possible that prostate cancer cells may also be influenced by increased VEGF secreted by adipocytes in obese states.

### 3.4. Adiponectin

Adiponectin, also called 30-kD adipocyte complement-related protein (Acrp30), adipoQ, APM-1, or gelatin-binding protein 28 (GBP28), is the most abundantly circulating adipokine, accounting for up to 0.05% of total plasma protein [40]. Two forms of adiponectin have been identified: full-length adiponectin (fAd) and a smaller globular fragment (gAd), which has been shown to have enhanced potency, although the latter has not been identified in the circulation. In contrast to other adipokines, circulating levels of adiponectin are negatively correlated with obesity (particularly central), BMI, visceral fat accumulation, and insulin resistance. Reductions in plasma adiponectin levels have also been observed in obesity-related states such as type 2 diabetes, cardiovascular disease, hypertension, and metabolic syndrome; indeed, adiponectin has been shown to ameliorate these disorders (see Kadowaki and Yamauchi [40] for a review).

These opposing properties of adiponectin to the majority of other adipokines have resulted in its proposal as an “anticancer” adipokine with respect to prostate cancer as well as other cancers such as breast and endometrial cancer [41]. In support of this hypothesis are the findings from a small case-control study that found plasma adiponectin levels to be significantly lower in subjects with prostate cancer compared to subjects with benign prostatic hyperplasia or healthy controls [42]. This study also found a negative association between plasma adiponectin and Gleason score and stage of prostate cancer.

Two receptor isoforms are known to exist for adiponectin: adiponectin receptor 1 (Adipo-R1) and adiponectin receptor 2 (Adipo-R2), which have distinct distributions and different affinities for the different forms of circulating adiponectin [40]. 5’-Adenosine monophosphate-activated protein kinase (AMPK) is one of the major signalling molecules responsible for mediating the metabolic effects of adiponectin and has also been implicated in prostate carcinogenesis [43].

Miyazaki et al recently demonstrated the presence of adiponectin receptors in the LNCaP-FGC, DU145, and PC-3 prostate cancer cell lines [27]. This study also identified JNK and signal transducer and activator of transcription 3 (STAT3) as common downstream effectors of adiponectin. Both JNK and STAT3 play crucial roles in obesity and insulin resistance and are also involved in the regulation of cell proliferation, differentiation, and apoptosis during various physiologic and pathologic events such as tumour development [44,45].

Our group has recently demonstrated the protein distribution of adiponectin receptors in benign and malignant human prostate tissue [46]. We also
showed that androgens, oestrogen, TNF-α, leptin, and adiponectin, which all display altered levels with obesity and are important in prostate cancer development, differentially regulate Adipo-R1 and Adipo-R2 in the LNCaP and PC3 prostate cancer cell lines. Interestingly, these effects were also specific to the cell line studied, having different effects depending on the androgen-receptor status of the cell line studied. These findings would suggest a complex role for adiponectin and its receptors in prostate cancer pathophysiology both directly and indirectly, via interaction between other hormones and cytokines.

fAd has also been shown to inhibit prostate cancer cell growth at subphysiologic concentrations [47] and to suppress proliferation stimulated by leptin, IGF-1, and dihydrotestosterone (DHT). Additionally, fAd also enhanced doxorubicin inhibition of prostate cancer growth in this same study. The investigation of adiponectin in prostate carcinogenesis is still in its infancy, and further studies are warranted to gain further insight into its role in this disease.

4. Discussion

Obesity is a complex disease state, resulting in a multitude of metabolic and endocrine disturbances and this may account for the inconsistencies seen in epidemiologic studies investigating the association between obesity and prostate cancer to date. Much evidence suggests that the presence of obesity may promote the progression of established prostate cancer rather than being a risk factor for the development of prostate cancer per se. The identification of adipose tissue as a metabolically active endocrine organ and the array of secreted adipokines would support such an association. In view of the numerous metabolic and endocrine sequelae of obesity, it is not inconceivable that certain cancers, in particular hormone-dependent cancers, may also be affected by obesity.

Adipokines represent a molecular mechanism whereby obesity exerts its effects on prostate tumour biology, by exposure of prostate cells to circulating adipokines or following into retropubic fat pad invasion. However, although a wealth of evidence demonstrates the effects of individual adipokines on prostate carcinogenesis, it is highly unlikely that the association between obesity and prostate cancer is due to the influence of a single adipokine in vivo. Obesity results in an alteration in the circulating profile of many factors, including adipokines and steroid hormones, and it is possible that changes in the relative ratios of these hormonal factors are more relevant. Furthermore, the identification of novel adipokines such as visfatin may also provide greater insight into this exciting area of research.

It is of interest that the two most abundant adipokines, leptin and adiponectin, have opposing effects. Whether relative ratios of these adipokines are related to prostate cancer risk or progression is yet to be investigated. This has been studied in patients with breast cancer, however, where an increased serum leptin-to-adiponectin ratio was found to be associated with aggressive disease [48]. Our group has also demonstrated an interaction between leptin and adiponectin in regulating the proliferation of prostate cancer cell lines (unpublished data).

Public health campaigns advocate lifestyle modifications such as dietary changes and exercise, and the benefits of weight loss in reducing the risks and complications of obesity-related comorbidities, eg, type 2 diabetes and cardiovascular disease. However, the benefits of such lifestyle changes may also improve prostate cancer prognosis and reduce the risk of developing other cancers associated with obesity (eg, colon). A recent study found that although physical activity had no effect on the overall risk of prostate cancer, recreational physical exercise was associated with a reduced risk of advanced prostate cancer and prostate cancer death [49]. To date there are no studies that investigate the effects of weight loss on disease progression in obese patients with prostate cancer, although it is possible that the beneficial effects of physical exercise on prostate cancer progression may in part be due to the consequences of weight reduction. Weight loss also reverses the circulating levels of leptin and adiponectin found in obese states; leptin levels rapidly decline with caloric restriction and weight loss [4], whereas weight reduction and improvement in insulin sensitivity increase adiponectin levels [50].

Variations in diet can occur due to differences in both the type of food consumed (eg, fat vs. carbohydrates vs. proteins, monounsaturated vs. polyunsaturated fat, animal meat vs. fruit and vegetables) and the amount (calorie content) of food consumed [10]. Most studies look at the association between a low-fat diet and prostate cancer risk rather than the progression of established disease and, unfortunately, it is not within the scope of this review to cover these in detail. Recently, numerous dietary supplements such as pomegranate juice, lycopene, and soy products have been proposed to reduce prostate cancer risk, but their effects on prostate progression are still to be determined.
Although there is no definitive evidence that advising patients with prostate cancer to adopt a low-fat, well-balanced diet will improve their prognosis, implementation of these modifications will undoubtedly improve their overall health and decrease their risk of cardiovascular disease, which remains the leading cause of death in Western populations.

5. Conclusions

Evidence suggests an association between obesity and prostate cancer progression that may occur at many levels. Adipokines may provide a molecular basis for this association, and future studies are required to investigate the complex interaction between these adipose tissue-derived factors with obesity, prostate cancer, and other hormones. A greater understanding of the pathogenesis of prostate cancer and adiposity could allow the development of new therapeutic markers, prognostic indicators, and drug targets. It may also provide scientific evidence to promote weight loss and other lifestyle modifications as beneficial adjuvant therapies for prostate and other cancers.

Conflicts of interest

None of the authors have any direct or indirect commercial financial incentive associated with publishing this article.

References


