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MINIREVIEWS

Is periprostatic adipose tissue associated with aggressive tumor biology in prostate cancer?

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Abstract

The prevalence of overweight and obesity and their health-related problems have been increasing. Obesity is increasingly recognized as a risk factor in different types of cancer in humans. The mechanisms supporting the link between obesity and cancer development have not been fully understood. Leptin, a circulating cytokine produced by adipocytes, may influence prostate cancer (PCa) progression in different ways. Body mass index seems to be an unreliable predictor for the development of PCa, but its influence on progression and poor oncological outcomes seems to be clear. Given the fact that abdominal fat is the most metabolically active fat, with different metabolic and paracrine effects, related anthropometric measurements may lead to a better estimation of PCa risk. Metabolically active periprostatic abdominal fat may also play an important role in releasing cytokines and growth factors that may promote tumor cell proliferation or even create a favorable environment for aggressive tumor biology. Different imaging measurements, *e.g.*, periprostatic adipose tissue (PPAT) thickness, may be significant predictors of PCa. Several genes in the PPAT of obese men have been identified to contribute to chronic immuno-inflammatory responses which eventually lead to cell cycle alteration with oncological potential. *In vitro* studies showed the importance of PCa and its interaction with its microenvironment particularly in patients with aggressive PCa. Different types of cytokines, such as interleukin-6, may promote a tumorigenic microenvironment. This article endeavors to review the current literature on the association of PPAT with aggressive tumor biology in PCa.

Key words: Prostate cancer; Obesity; Periprostatic fat

Core tip: Globally, prostate cancer (PCa) is highly prevalent. Although the prevalence of PCa is similar across different populations, major differences in PCa incidence and mortality are seen worldwide. A contribution of environmental factors, such as obesity, may play an important role. Most studies used body mass index as a factor of obesity. However, only visceral fat is metabolically active. In a study by van Roermund *et al*, periprostatic fat measured on a computed tomography scan correlated with tumor aggressiveness. In this review, we aim to give more insight into the relationship between periprostatic fat and Pca aggressiveness by reviewing the recent literature.

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INTRODUCTION

Over the past few decades, the prevalence of overweight and obesity have been increasing in developed countries[1]. Obesity is currently seen as a serious health problem in particularly well-developed populations. More

recently, it has been hypothesized that obesity could potentially influence the risk of developing cancer. Several studies already showed a correlation between obesity and different types of cancer[2-4]. However, the relationship between obesity and the risk of developing prostate cancer (PCa) is still unclear, as studies are inconsistent in their outcome[5,6]. The incidence of clinically significant PCa is highest in well-developed countries, and in Europe, PCa is the second most common cause of cancer-related death in men[7].

Although many risk factors for PCa are well known, including age, ethnic background, and family history, the mechanisms of the interactions between lipids and carcinogenesis are not fully understood. Multiple studies suggest an important role for metabolic active periprostatic adipose tissue (PPAT) in the risk of developing PCa[8-12]. This review specifically considers the relationship between PPAT and the risk of developing aggressive PCa, and discusses the underlying mechanisms and clinical consequences.

RESEARCH

For this review a literature search in PubMed was performed using the MeSHsearch terms; "periprostatic fat", "obesity" linked with "prostate cancer". Studies relating to periprostatic adipose tissue and PCa were selected, and limited to articles in the English language. Studies identified in references and considered relevant were also included.

OBESITY AND PROSTATE CANCER

Obesity is considered as one of several factors potentially related to the development of clinically significant PCa. Earlier postmortem research showed a high prevalence of PCa, occurring in approximately 80% of men > 70 years of age who died from other causes[13,14]. The high prevalence of PCa in elderly males supports a hypothesis that progression of latent PCa to clinically significant PCa might be associated with environmental and lifestyle factors. In particular, abdominal obesity may be an important factor influencing progression of latent PCa to clinically significant PCa, rather than development of latent disease.

Evidence that body mass index (BMI) is related to a higher incidence of PCa is still inconsistent. A prospective cohort study in 900000 adults showed a significant positive linear trend in death rates with increasing BMI for all cancers, including PCa[3]. In that study, men with a BMI of at least 35.0 appeared to have a significantly elevated relative risk of cancer-related death compared with normal weight males. In relation to these data, a systematic review of MacInnes evaluated the association between anthropometric measurements and the risk of PCa[15]. In that meta-analysis a weak positive correlation between the risk of PCa and BMI and waist-hip ratio (WHR) was found. Moreover, subgroup analysis showed a positive correlation between the risk of advanced PCa and BMI and WHR, supporting the hypothesis that obesity might influence PCa progression or tumor biology. In contrast, no direct correlation between PCa and weight was found in the study.

A large European prospective cohort study in 150000 men suggested that higher waist circumference and WHR may be associated with increased risk of advanced PCa and high-grade PCa amongst individuals with lower BMI. No association was seen in males with higher BMI levels, suggesting that abdominal adiposity mainly played an important role in influencing PCa[16]. An explanation for the inconsistency in the results can be found in the fact that BMI, or even WHR, are inadequate measures of obesity as they include adipose and non-adipose body components. Given the fact that abdominal fat is the most metabolically active fat tissue, we should explore other methods for estimation of adipose tissue, such as fat distribution, which may eventually link obesity to PCa.

Several studies have correlated obesity with higher PCa grade and poorer oncologic outcomes[17-20]. Capitanio *et al*[17] showed that BMI was independently associated with PCa volume at radical prostatectomy. These results were confirmed by Freedland *et al*[18] in over 2200 patients treated with radical prostatectomy, and showed that obese males were more likely to have high-grade tumors. In addition, more adverse pathological features and a higher risk of biochemical recurrence were seen in obese patients. Significantly higher rates of PCa recurrence over time were observed in obese patients (BMI $\geqslant$ 30) compared with their non-obese counterparts in two other studies[19,20].

Possible mechanisms linking obesity and cancer involve endocrine disturbances such as increased serum estrogen, insulin, insulin-like growth factor and leptin, and decreased free testosterone[21-25]. However, the mechanisms by which obesity leads to an increased risk of PCa are not known, and may occur at multiple levels. Recently, different *in vitro* studies on leptin have been performed. Leptin is a cytokine produced by adipocytes. Like insulin, leptin controls body weight homeostasis through food intake and energy balance[26]. Circulating serum leptin levels correlate with body fat in humans. Hoda *et al*[21] showed that a chronic systemic increase in leptin might enhance the growth of prostate or other cancer cells by activation of the mitogen-activated protein kinase pathway. Moreover, leptin stimulated growth of breast, esophagus, and prostate cancer cell lines in different studies[24,27,28]. In addition, leptin may accelerate PCa progression by promoting androgen-independent cell proliferation[25].

PERIPROSTATIC ADIPOSE TISSUE

PPAT surrounds the prostate capsule[29]. In an earlier study of Hong *et al*[30], 100 prostatectomy specimens were analyzed, and showed that adipose tissue covering the prostatic surface was present in 48% of prostates, with the least adipose tissue found posteriorly. By analyz-

ing PPAT, valuable new insights could be attributed to the role of adipose tissue in PCa pathophysiology. This particular adipose tissue is not only used for storage of triglycerides, but also plays a role in releasing cytokines and growth factors that may promote tumor cell proliferation or play a role in creating a favorable environment for aggressive tumor biology[10,11,31,32]. Finley *et al*[10] analyzed PPAT of patients who underwent a radical prostatectomy. They suggested that once cancer cells extend beyond the prostate capsule, these PPAT-secreted factors, may influence the phenotypic behavior of malignant cells *via* extracellular matrix components or direct cell-to-cell contact. This cellular mechanism and PPAT-secreted factors have been proposed in a limited number of different publications which we will discuss below.

IMAGING

Only three studies used *in vivo* imaging techniques in investigating the relationship between PPAT and PCa. van Roermund *et al*[8] retrospectively analyzed whether periprostatic fat and subcutaneous fat measured by computed tomography correlated with advanced PCa stage in a group of patients who underwent external radiotherapy or brachytherapy for localized PCa with different risk classifications according to Ash *et al*[33]. A significantly larger total periprostatic fat area and higher periprostatic fat density was seen in patients with high risk PCa, compared with low and intermediate risk patients[8]. An association was found between more periprostatic fat and higher periprostatic fat density, and prostate-specific antigen (PSA) $\geqslant$ 10 ng/mL, a T3 tumor, and a Gleason score $\geqslant$ 8. A different study, analyzing PPAT as a marker for PCa aggressiveness in patients only treated with brachytherapy, showed no correlation between PPAT and advanced PCa stage[34]. A confounding factor might be that brachytherapy is mainly used in low-risk PCa patients, which might explain the absence of a correlation in this particular study.

Bhindi *et al*[9] evaluated whether PPAT thickness on transrectal ultrasound could be a predictive factor for the detection of PCa in men with no prior diagnosis of PCa. Besides known predictors of PCa, such as older age, African ethnicity, family history of PCa, abnormal digital rectal examination (DRE) and elevated PSA level, PPAT thickness was also a significant predictor for detection of PCa or high-grade PCa. They suggested that for each millimeter increase in PPAT thickness, the odds of detecting any PCa or high-grade PCa increased by 12% and 20%, respectively. So beside other clinical parameters, including age, abnormal DRE and PSA level, PPAT may have a clinically significant role in diagnostic algorithms for PCa in the future[9].

GENETICS

The individual genome represents the starting point for transformation of prostate epithelial cells and its microenvironment. Knowledge of the PPAT genetic profile may uncover more about the relationship with PCa tumor biology. Until now, only one study reported on the gene expression of PPAT in relation to PCa. Ribeiro *et al*[35] aimed to determine the spectrum of genes expressed in PPAT to evaluate the influence of obesity on PCa and vice versa. PPAT was obtained from 18 patients, with an equal distribution of obese and lean men. Patients underwent a retropubic radical prostatectomy for PCa (organ-confined and extra-prostatic) or open prostatectomy in the case of benign prostatic hyperplasia. Results showed that several genes in the PPAT of obese men contributed to chronic immuno-inflammatory responses, *i.e.*, anti-lipolytic, lipogenic, proliferative and anti-apoptotic activities. These immuno-inflammatory responses lead to white adipose tissue overgrowth and alteration of the cell cycle to promote oncogenesis[35,36]. These findings support the importance of PPAT and the presence of a complex relationship between obesity and PCa.

MICROENVIRONMENT

Tumor cell progression depends on the tumor characteristics as well as on the surrounding microenvironment. Moreover, after highlighting the importance of the genetic profile, we should not underestimate the influence of interactions between tumor cells and their microenvironment[10,31,37-39]. The microenvironment is able to influence the proliferation, migration and metastatic behavior of tumor cells by modulating the extracellular matrix and growth factor production[40]. In breast cancer, a paracrine effect of adipose tissue on the microenvironment of the tumor is already associated with poorer oncologic outcomes[41]. Tokuda showed in an *in vitro* study that PCa cells grow differently in an adipocyte-rich environment, compared with control cultures[39]. In particular, higher cytokine expression in PCa cells was seen when cultured in an adipocyte-rich environment.

A pilot study by Venkatasubramanian *et al*[42] on PPAT from obese PCa patients aimed to explore whether PPAT from obese patients differed from that of lean patients, with specific attention to differences in the microenvironment. *Ex vivo* magnetic resonance imaging and histology were used on the collected tissue of patients who underwent a radical prostatectomy for primarily low-grade PCa. PPAT from obese patients showed significantly increased proliferation of PCa, compared with PPAT from lean patients.

Visceral adipose tissue differs from peripheral adipose and secretes different types of cytokine-like adipokines, leptin and adiponectin, numerous inflammatory mediators, interleukins, chemokines and growth factors. Finley *et al*[10] explored the association of cytokines and growth factors secreted by PPAT in patients with aggressive PCa. In this study, significantly higher levels of interleukin-6 (IL-6) were shown in PPAT of patients with higher grade tumors. Higher IL-6 levels were associated with downstream activation of signal transducer and activa-

tor of transcription 3 phosphorylation, which promotes cell cycle progression, tumor invasion and host immune system evasion. This suggests that PPAT modulates PCa aggressiveness by serving as a source of IL-6. This modulating role of PPAT is confirmed by Ribeiro *et al*[11], who showed locally increased activity of matrix metalloproteinase (MMP), a proteolytic enzyme facilitating and promoting PCa cell survival and migration. Interestingly, higher levels of MMP9 were seen in obese men with esophageal adenocarcinoma, and is associated with poor tumor differentiation in these patients[43]. In PCa, MMP activity in PPAT is significantly increased compared with that in the PPAT of patients with benign prostatic hyperplasia[31].

CONCLUSION

Though limited, studies evaluating the association between PPAT and PCa describe evidence for an interaction between PCa and its surrounding tissues. Data suggest that local adipose tissue can alter the behavior of cancer cells in different ways. Microenvironment-related release of factors such as cytokines and interleukins, play an important role in promoting survival and migration of PCa cells, and thus PCa progression. Different genes in PPAT of obese patients also contribute to a favorable environment for tumor growth. Given that PPAT thickness can be related to PCa aggressiveness, this may represent a diagnostic tool with important prognostic value, since BMI is unreliable as a prognostic factor. The findings of this review of the literature should promote future studies to further investigate the value of PPAT in PCa etiology and its relationship to the development of aggressive PCa. New therapeutic strategies could be developed, and more studies of the diagnostic value of PPAT should be pursued.

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