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

Den Hollander PP *et al*. Obesity and prostate cancer

Philip P Den Hollander, Kevin LJ Rademakers, Joep GH van Roermund

Philip P Den Hollander, Kevin LJ Rademakers, Joep GH van Roermund, Department of Urology, Maastricht University Medical Centre, 6202 AZ Maastricht, The Netherlands

**Author contributions:** All the authorssolely contributed to this paper.

**Correspondence to: Joep GH van Roermund, MD, PhD,** Department of Urology, Maastricht University Medical Centre, P Debyelaan 25, POB 5800, 6202 AZ Maastricht, The Netherlands. joep.van.roermund@mumc.nl

**Telephone:** +31-43-3877258 **Fax:** +31-43-3875259

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**Abstract**

The prevalence of overweight and/or obesity and its health related problems has been increasing. Obesity is increasingly recognized as a risk factor in different types of cancer in humans. Until now, mechanisms supporting the link between obesity and cancer development are not 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 worse oncological outcomes seems to be clear. Given the fact that abdominal fat is the most metabolically active fat, with different metabolic and paracrine effects, other methods for anthropometric measurements can lead to a better estimation of PCa risk profiles. Metabolic active periprostatic abdominal fat may also play an important role in releasing cytokines en growth factors that may promote tumor cell proliferation or even creates a favorable environment for aggressive tumor biology. Different imaging techniques, *e.g.*, periprostatic adipose tissue (PPAT) thickness, can be significant predictors in PCa. Several genes in PPAT of obese men are identified which contribute to chronic immuno-inflammatory responses which eventually leads to cell cycle regulation with oncological potential. *In vitro* studies showed the importance of PCa and interaction with its microenvironment even more in patients with aggressive PCa. Different types of cytokines like interleukin-6 may create protumorigenic microenvironment. This article endeavors to review the current literature on the relation with PPAT and the link with aggressive tumor biology

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**Key words:** Prostate cancer; Obesity; Periprostatic fat

**Core tip:** Globally, prostate cancer is highly prevalent. Although the prevalence of Pca is similar across different populations, enormous differences in prostate cancer (PCa) incidence and mortality over the world are seen. A contribution of environmental factors, like obesity may play an important role. Most studies used body mass index as a factor of obesity. However only the visceral fat is metabolic active. In a study of van Roermund *et al*, periprostatic fat measured on a computed tomography-scan correlated with tumour aggressiveness. With 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 decades, prevalence of overweight and obesity have been increasingly higher in developed countries[1].Obesity is currently seen as a serious health problem to particularly well-developed populations. More recently, it has been hypothesized that obesity could potentially influence the risk of developing cancer. Several studies already showed the correlation between obesity and different types of cancer[2-4]. However, the relationship between obesity and the risk of developing prostate cancer is still unclear, as studies are inconsistent in their outcome[5,6]. The incidence of clinically significant prostate cancer (PCa) is highest in well-developed countries and in Europe PCa is the second cause of cancer-related death in men[7].

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

**METHODS**

For this review a literature search in Pubmed was performed using the search (Mesh) terms; “periprostatic fat”, “obesity” linked with “prostate cancer”. Studies relating to periprostatic adipose tissue and prostate cancer were selected, 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 high PCa 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 to clinically significant PCa might be associated with environmental and lifestyle factors. Particularly abdominal obesity might be an important factor influencing progression of latent to clinically significant PCa, rather than development of latent disease.

Evidence that body mass index (BMI) is related to higher incidence of PCa is still inconsistent. A prospective cohort study in 900.000 adults showed a significant positive linear trend in death rates with increasing body-mass index for all cancers, including PCa[3]. In this study, men with a BMI of at least 35.0 appeared to have a significantly elevated relative risk of cancer-related death compared to normal weight males. In concordance with these data, a systematic review of Mac Innes*.* evaluated the relationship between anthropometric measurements and the risk of PCa[15]. In this meta-analysis a weak positive correlation between the risk of PCa and BMI and waist-hip ratio (WHR) was found. Moreover, a subgroup analysis showed a positive correlation between the risk of advanced PCa and BMI and WHR, supporting the hypothesis that obesity might influence progression or tumor biology of PCa. In contrast, no direct correlation between PCa and weight was found in this study.

A large European prospective cohort study in ± 150.000 men suggested that higher waist circumference and WHR may be associated with increased risks of advanced PCa, and high-grade prostate cancer amongst individuals with lower BMI. No association was seen in males with higher BMI levels, suggesting that mainly abdominal adiposity plays an important role in influencing PCa[16]. An explanation for inconsistency in study results with regard to this topic can be found in the fact that BMI, or even WHR, reflect an inadequate measure of obesity by combining 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, like fat distribution, which may link eventually link obesity to PCa.

Several studies relate obesity to higher prostate cancer grade and worse oncologic outcomes[17-20]. Capitanio *et al*[17] showed that BMI is independently associated with PCa volume at radical prostatectomy. These results were confirmed by Freedland *et al*[18]*,* showing that obese males had high-grade tumors in over 2200 patients treated with radical prostatectomy. In addition, more adverse pathological features and higher biochemical recurrence risk were seen in obese patients. Significantly higher rates of PSA recurrence over time were observed in obese patients (BMI ≥ 30) compared to the non-obese counterparts[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 is 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 human. Hoda *et al*[21] showed that 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 showed growth stimulation in breast, esophagus, and PCa with this mitogenic effect on cancer cell lines in different studies[24,27,28]. In addition, leptin may accelerate prostate cancer progression by leptin 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, showing that adipose tissue covering the prostatic surface was present in 48% of the prostates with the least adipose tissue found posteriorly. By analyzing periprostatic adipose tissue, 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 of periprostatic adipose tissue has been, though limited, proposed in different publications which we will discuss further on.

**IMAGING**

Only three studies used *in vivo* imaging techniques in relating PPAT and PCa. van Roermund *et al*[8] retrospectively analyzed whether periprostatic fat and subcutaneous fat measured on computed tomography (CT-scan) correlates with advanced PCa stage in a group of patients who underwent external radiotherapy or brachytherapy for localized prostate cancer in patients 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 to low and intermediate risk patients[8]. An association in odds ratio between more periprostatic fat and higher periprostatic fat-density was found in PSA ≥ 10, having a T3 tumor and having a Gleason score ≥ 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.

Bhindy *et al*[9] evaluated whether PPAT thickness on transrectal ultrasound (TRUS) could be a predicting factor for the detection of PCa in men with no prior diagnosis of prostate cancer. Besides known predictors on detection of PCa like older age, African ethnicity, family history of prostate cancer, abnormal digital rectal examination (DRE) and elevated PSA level, also PPAT thickness was a significant predictor for detection of PCa or high-grade PCa. They suggested that for each millimeter increase in PPAT thickness the odds for detecting any PCa and high-grade PCa increased ± 12% and ± 20%, respectively. So beside other clinical parameters, including age, 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 prostate epithelial cells and its microenvironment. Knowledge of the PPAT genetic profile may uncover more of the relationship with PCa tumor biology. Until now, only one study reported on gene expression of PPAT in relationship with 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 case of benign prostatic hyperplasia. Results showed that several genes in PPAT of obese men contribute 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 alters cell cycle regulation with oncogenic potential[35,36]. These findings support the importance of PPAT and 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 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 worse oncologic outcomes[41]. Tokuda showed in an *in vitro* study that prostate cancer cells grow differently in an adipocyte-rich environment, compared to control cultures[39]. In particular, more cytokine expression of prostate cancer cells were seen when cultured in an adipocyte-rich environment.

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

Visceral adipose tissue differs from peripheral adipose and secretes different types of cytokines-like adipokines, leptin and adiponectin, numerous inflammatory mediators, interleukins, chemokines and growth factors. Finley explored the association of cytokines and growth factors secreted by periprostatic adipose tissue in patients with aggressive PCa[10]. 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 are associated with downstream activation of the Signal Transducer and Activator of Transcription 3 (STAT3) 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*,* who showed a locally increased activity of matrix metalloproteinase (MMP), a proteolytic enzyme facilitating and promoting prostate cancer cell survival and migration[11]. Interestingly, higher levels of MMP9 were seen in obese men with oesophagal adenocarcinoma and is associated with poor tumor differentiation in these patients[43]. In prostate cancer, MMP activity in PPAT is significantly increased compared to PPAT of patients with benign hyperplasia[31].

**CONCLUSION**

Though limited, studies evaluating the relation of PPAT and PCa describe a certain evidence of PCa and interaction with its surrounding tissues. Data suggest that local adipose tissue can alter behavior of cancer cells in different ways. Microenvironment releasing factors like cytokines and interleukins play an important role in promoting survival, migration and in this way development into PCa with poor prognosis. Also identification of different genes in PPAT of obese, contribute to tumor favorable environment. Given that PPAT thickness can be related to PCa aggressiveness, this can be a diagnostic tool with important prognostic value since BMI is unreliable prognostic factor. The findings of this review of literature should promote future studies to further investigate the value of PPAT in prostate cancer and its relationship to develop aggressive PCa. New therapeutic strategies can be developed and better understanding of diagnostic value of PPAT should be pursued.

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