

# Obesity, diabetes and aggressive prostate cancer hormone-naïve at initial diagnosis

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**Introduction.** Epidemiologic studies have implicated obesity in prostate cancer (PCa) development and aggressiveness; nevertheless, no clear consensus has been reached. The aim of the research was to investigate the association of obesity with PCa, hormone-naïve at initial diagnosis.

**Methods.** A retrospective analysis of 266 patients undergoing prostate biopsy at our institution, between 2006 and 2009, was conducted. We examined obesity and PCa association in 133 patients with PCa, hormone-naïve at initial diagnosis, versus 133 age-matched controls. Men with incomplete data available, a history of hormone therapy or chemotherapy, prostate or bladder surgery were excluded.

**Results.** Obesity was significantly associated (OR 2.25) with aggressive PCa (Gleason score  $\geq 7$ ) and inversely related (OR 0.35) to non-aggressive PCa (Gleason score  $\leq 6$ ). Particularly, obesity in diabetic patients was significantly linked with aggressive PCa (OR 4.17). No association was noted between obesity and PCa development.

**Conclusions.** In our study, obese patients, particularly in combination with diabetes mellitus (DM), were more likely to present with more aggressive PCa. Further research with larger samples should be done to confirm these associations and to stabilize future prevention strategies.

**Key Words:** prostate cancer ♦ obesity ♦ diabetes mellitus ♦ prevention

## INTRODUCTION

Epidemiological studies have implicated metabolic alterations, either separately or in combination, in prostate cancer (PCa) development and aggressiveness; nevertheless, no clear consensus has been reached [1].

Recent works have reported that obesity either increased or was not associated with the risk of advanced or high-grade tumor [2-6].

Several studies have reported decreased PCa risk among patients with type II diabetes mellitus (DM), while others found either no protective effect or even an elevated risk.

Thus, controversy still persists regarding the influence of DM and obesity on PCa detection and development [7-11].

The aim of this study was to investigate the asso-

ciation of obesity with PCa, hormone-naïve at initial diagnosis.

## METHODS

A retrospective analysis of 266 patients undergoing prostate biopsy at our institution, between 2006 and 2009, was conducted.

We examined associations of obesity in 133 patients with PCa diagnosis, with positive biopsy, versus 133 age-matched controls, with negative biopsy. Patients with negative biopsy for PCa, but with atypical small acinar proliferation (ASAP), atypical adenomatous hyperplasia/adenosis, high-grade PIN (HGPIN), were excluded from evaluation.

All men with incomplete data, a history of hormone therapy or chemotherapy, prostate or bladder surgery were excluded.

The cases and controls were divided into two cohorts on the basis of body mass index (BMI): BMI <30 (non-obese) and BMI ≥30 (obese) respectively. BMI was calculated as the weight in kilograms divided by height in meters squared. The cases were also classified at diagnosis according to the Gleason grading system as high-grade (Gleason score ≥7) or low-grade (Gleason score ≤6).

Differences in the distribution of continuous variables between the study groups were described in terms of the median or mean ± standard deviation (SD), and assessed for statistical significance using Mann-Whitney rank sum test or t-test. Differences in the distribution of categorical variables were expressed as the number of patients (frequencies and percentage) and evaluated using the chi-square test of independence; however, when low cell counts were found, Fisher's exact test was utilized. A p-value less than 0.05 was considered statistically significant.

## RESULTS

Cases and controls were matched by age (69 years *vs.* 68 years respectively,  $p = 0.322$ ). Obesity was not associated with PCa overall, but was significantly related to PCa aggressiveness. Obesity, particularly, was significantly associated (OR 2.25,  $p < 0.05$ ) with aggressive PCa (Gleason score ≥7) and inversely related (OR 0.35,  $p < 0.05$ ) with non-aggressive PCa (Gleason score ≤6) (Figure 1).

Moreover, in diabetic patients, after stratification by obesity, DM was associated with aggressive PCa, only in obese cases (OR 4.17). In non-obese men, no association was noted between DM and PCa, irrespective of grade.

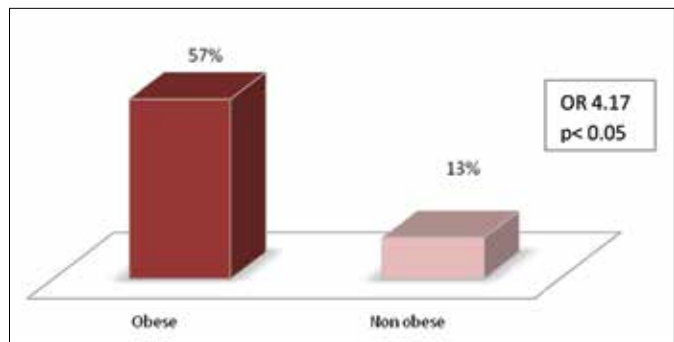
## DISCUSSION

The aim of this study was to examine, in a retrospective analysis of 266 patients undergoing prostate biopsy, the association between obesity and PCa, with further stratification of cases into subgroups according to body habitus (BMI) and Gleason grade.

### Obesity and PCa aggressiveness

The relationship between PCa and obesity has produced conflicting results and is still a matter of debate [12, 13, 14].

Recent studies indicate that obesity is associated with an increased risk of high-grade disease and a reduced risk of low-grade disease [1, 12, 15, 16, 17]. Similarly, in our study, we found that obesity was significantly associated with increased high-grade PCa and reduced low-grade PCa. Particularly, obese



**Figure 1.** DM and PCa aggressiveness in obese cases versus non-obese cases. After stratification by obesity, DM was associated with aggressive PCa only in obese cases (OR 4.17,  $r = 0.41$ ,  $p < 0.05$ ). In non-obese men, no association was noted between DM and PCa, irrespective of grade.

men had a more than two-fold increased risk of developing high-grade disease, compared with their non-obese counterparts.

Several hypotheses can be suggested to explain the association between obesity and high-grade PCa. Data from the literature indicate that obesity could be associated with biological changes (e.g. increased inflammation, insulin resistance, angiogenesis, cell migration) and modification of adipokine levels related to a more aggressive PCa phenotype.

Specifically, adipose tissues release reduced anti-inflammatory adipokines (e.g. adiponectin) and increased inflammatory adipokines (e.g. leptin, resistin), causing a chronic inflammatory state and increased cancer progression [16, 18, 19].

The literature suggests that reduced adiponectin levels may be related to increased PCa aggressiveness [16, 20]. It has been reported that adiponectin is involved in the regulation of energy homeostasis (particularly glucose and lipid metabolism), in inhibition of inflammation, atherogenesis, angiogenesis and cell migration [21, 22, 23]. Its serum levels are decreased in obesity, coronary artery disease and malignancies such as PCa, with a negative association with histological grade and stage of disease [24]. In vitro adiponectins inhibit cell growth and proliferation in the prostate and antagonize the proliferative effects of leptin and IGF-I in androgen-independent PCa [25].

Leptin acts directly on prostate cells to affect steroid activity, cell cycle regulation, and insulin activity [26]. Leptin, particularly, increases lipolysis, insulin sensitivity, inflammation and thromboembolism [21]. It influences cellular differentiation and PCa progression, cell migration, tumor angiogenesis and advanced PCa, through the induction and activation of pro-angiogenic factors [16, 27-30].

Resistin promotes inflammation and carcinogenesis by inducing endothelial cells and macrophages to produce oxygen free radicals, TNF- $\alpha$ , interleukin (IL)-12 and IL-6 [21, 31, 32].

It has been hypothesized that low adiponectin and higher leptin and resistin levels, observed in obese patients, may be associated with aggressive PCa.

A recent study confirmed these hypotheses indicating that high leptin levels can be correlated with higher stage and grade of PCa, while high adiponectin levels are correlated with lower stage and grade of PCa. This suggests that low adiponectin and high leptin levels observed in obese patients could be associated with the development of high-grade PCa [16].

### Obesity, DM and PCa aggressiveness

Obesity is a well-known risk factor for type 2 DM. Given that obesity is a factor for the development of both DM and high-grade PCa, we investigated whether the association between DM and high-grade disease varied with obesity in our Italian cohort [10]. In the present study of 266 men undergoing prostate biopsy, we found that DM was associated with high-grade PCa, only in the obese subjects.

These findings, reported similarly by other recent studies, suggest that DM might be associated with more aggressive disease only in obese men, with DM possibly conferring no risk in non-obese men, but increased risk in obese men [8, 10, 33].

Recent data obtained from 119315 men with DM, to examine the relationship between metformin exposure and the risk of PCa, indicate that there was no association between metformin use and the risk of PCa regardless of cancer grade [34]. However, the effect of anti-diabetic agents in PCa development, aggressiveness and progression remained unclear. Specifically, the literature reported a conflicting relationship between metformin use and PCa, demon-

strating a decreased risk or increased risk or no association with PCa [35-40].

Another potential factor leading to the disparities observed may be associated with the combined effect of obesity and DM on PCa aggressiveness (not evaluated by Margel et al.).

Thus, it is likely that a combination of the above biological and behavioral factors may be responsible for the discrepant association between DM and high-grade PCa.

Several hypotheses can be suggested to explain the obesity influence on the association between DM and high-grade PCa.

The link between obesity, type 2 DM and PCa has a strong association to insulin resistance, hyperinsulinemia, reduced levels of IGFBP (insulin-like growth factor binding proteins), increased bioavailability of IGF-1 (insulin-like growth factor-1), steroid and peptide hormones, and inflammatory markers [3, 41, 42]. We previously reported an important role of inflammation and immune system as a regulator in PCa physiology and pathology [43, 44].

Moreover, obesity and type 2 DM have been demonstrated to have a positive association with both the risk of cancer and cancer-related mortality [45, 46].

The chronic inflammation and oxidative stress associated with DM and obesity may also contribute to PCa development and progression [47, 48].

### CONCLUSIONS

In our study, obese patients were more likely to present with more aggressive PCa, particularly in combination with DM. Metabolic derangements may increase oxidative stress and cause a permanent pro-inflammatory state that predisposes to aggressive PCa. Further research with larger samples should be done to confirm these associations and to stabilize future prevention strategies.

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