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Association between Biomarkers of Obesity and Risk of High-Grade Prostatic Intraepithelial Neoplasia and Prostate Cancer - Evidence of Effect Modification by Prostate Size

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Abstract

Prostate enlargement is common with aging and obesity. We investigated the association between obesity and prostate cancer controlling for differential detection related to prostate enlargement. In an analysis of 500 men, we found body mass index, waist-hip ratio, and blood leptin levels were significantly associated with high-grade PC, but only among men without prostate enlargement. Leptin was also significantly associated with high-grade prostatic intraepithelial neoplasia (HGPIN) in the absence of prostate enlargement. Our results suggest obesity advances prostate carcinogenesis, and that detection biases at prostate biopsy may explain past inconsistencies in the association between obesity and PC.

Keywords

prostate cancer; high-grade prostatic intraepithelial neoplasia; obesity; bias; human

1. Introduction

Interest in the relationship between obesity and prostate cancer (PC) derives from the possibility that there could be a modifiable risk factor this common and sometimes fatal disease [1]. Several studies report that obesity increases the risk of advanced PC, PSA recurrence following treatment, and prostate cancer mortality [2–6]. Weight gain since age 18 years has similarly been associated with PC mortality [7]. However, the duration of PC survivorship has increased since broad utilization of the PSA test, and most patients are diagnosed with localized or low-grade prostate cancer. The relationship between obesity and PC risk in the PSA era remains in question, with several studies suggesting that obesity is associated with a lower risk of localized or low-grade PC [8, 9]. Similarly, Type 2 diabetes

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(T2D) is strongly associated with obesity, and studies report either a higher or a lower PC risk with continued follow-up after a T2D diagnosis [10–13].

The reasons for such contradictory relationships between obesity and PC are unknown. Excess adiposity has a global impact on insulin activity, inflammation, steroid metabolism, angiogenesis, and adipocytokine levels [14, 15]. These pathways are not mutually exclusive, and any number of obesity-affected pathways may be involved or interact within specific phases of prostate carcinogenesis [16, 17]. Unfortunately, common measures of obesity such as body mass index (BMI), waist circumference (WC), and waist-hip ratio (WHR) are non-specific and provide little information on which pathways might play a substantive role in prostate carcinogenesis. Aside from the challenges related to obesity measurement, stage-specific associations between obesity and PC may be caused by differences in the ability to detect prostate cancer between obese and non-obese men. For example, several studies report that obese men have lower blood PSA levels, such that it may be more difficult to detect early-stage PC among obese men [18, 19]. Alternatively, the frequency of PSA testing increases with greater healthcare utilization [20, 21], possibly creating more opportunities to detect PC among obese men with diabetes or other healthcare needs. Indeed, enhanced screening near the time of diabetes diagnosis was thought to account for at least a part of the decreased prostate cancer risk found after extended follow-up, as latent disease is culled early from the clinical population [22]. Finally, obesity is a common comorbidity associated with prostate enlargement [23], and data from the Prostate Cancer Prevention Trial (PCPT) suggests that it is more difficult to detect small PC lesions at biopsy among men with a larger prostate volume [24]. Given that obesity could affect PC detection as well as perhaps the stage or grade at diagnosis, further understanding the biological basis of any obesity-PC relationship will require future studies to better control for the effects of obesity on prostate cancer detection.

The purpose of this analysis is to investigate the association between obesity-related biomarkers and PC while controlling for healthcare access, comorbidities related to obesity, and potential detection biases derived from prostate enlargement. Obesity biomarkers under investigation include leptin, an adipocytokine released directly from adipocytes to communicate energy storage levels and which may have direct effects on prostate cancer cells through leptin receptor activity or cancer cell metabolism. Additionally, adiponectin production from adipocytes decreases with obesity, and plays a role in both insulin sensitivity and the inflammatory response [25–29]. Estradiol may be involved in prostate cell regulation and prostate growth, and estradiol levels increase in obese men through CYP19 (aromatase) activity in adipose tissue. C-peptide is released in molar equivalents to insulin and provides a marker of obesity related to insulin activity and regulation. In studying the association between these biomarkers and PC, we include analyses of the PC precursor high-grade prostatic intraepithelial neoplasia (HGPIN) to consider the effects of obesity on the earliest phases of prostate carcinogenesis [30]. Our results may provide further insight into the role of obesity from the early through later phases of prostate carcinogenesis.

2. Materials and Methods

2.1 Study Design

The Nashville Men’s Health Study (NMHS) is a multi-centered, rapid-recruitment protocol to investigate the clinical, genetic, and behavioral determinants of prostate cancer detection, progression, and treatment outcomes. All recruitment and data collection protocols were approved by IRBs at Vanderbilt University and the Tennessee Valley Veteran’s Administration. Men referred for prostate biopsy to Vanderbilt University Medical Center, a large community urology practice (Urology Associates, Nashville, TN), and the Tennessee

Valley Veterans Administration Medical Center were targeted for recruitment. These urology clinics receive referrals from physicians throughout metro Nashville, TN, and are the primary providers of diagnostic services for urologic disease in the area. Recruitment occurred prior to the prostate biopsy procedure, thus avoiding biases associated with treatment or knowledge of their disease status. Approximately 90% of eligible men approached for recruitment consented to participate. Exclusion criteria included age less than 40 years, a prior prostate cancer diagnosis, prior prostate surgery, current androgen supplementation use, or English insufficiency for informed consent.

2.2 Blood Collection

A blood sample was collected from participants at recruitment, and prior to prostate cancer diagnosis or treatment. Blood samples were refrigerated immediately and hand-delivered cold on that day to our lab at Vanderbilt University for processing. Serum aliquots were stored frozen at −86° C.

2.3 Measurements

All body size measures were obtained at the time of recruitment by trained research staff. Weight (kg) (no shoes, hospital gown) was measured on a calibrated scale, and height (within 0.1 cm) was measured by stadiometer. Body circumferences were measured using an anthropometric tape measure with built-in tension meter (Gullick II) to ensure an even tension was administered to the tape across participants. Waist circumference was measured at the plane across the iliac crest and usually represents the narrowest part of the torso. Hip circumference was measured at the maximum posterior extension of the buttocks. Two measurements at each site are made in rotational order, with a third measurement if the first two differed by more than 1 cm. Waist-to-Hip ratio (WHR) was calculated from the average waist and hip circumference for each participant. Participants also provided the time of their last food and beverage intakes.

2.4 Medical chart review

Data abstraction from urology, surgery, and pathology medical reports included PSA test history, the number of prior biopsies, number of prostate cores collected at biopsy leading to recruitment, and prostate size (ml) at biopsy. Biopsy Gleason score was abstracted for participants diagnosed with cancer to define tumor aggressiveness. A single pathologist reviewed over 90% of biopsies, and follow-up chart review for 216 prostate cancer cases found that no cases were diagnosed with metastatic disease at recruitment. All HGPIN cases were reviewed by a single uropathologist using criteria defined by Epstein [31]. Subjects are instructed to make a list of all current medications at home or to bring their medications to this clinic visit to be entered into the subject’s computerized medical record.

2.5 Biomarker Sub-Study

We created a biomarker sub-study of 500 NMHS participants to investigate the associations between cancer and candidate blood and urine biomarkers. The sub-study drew from NHMS participants recruited between 2003 and December 2008, and included four diagnostic case groups: HGPIN, low-grade PC, high-grade PC, and a control group without prostate cancer, HGPIN, or other findings (e.g., atypia) that are suspicious for PC. Since our focus was on early events in PC toward a prostate cancer prevention strategy, we selected all 140 HGPIN patients that were available at that time for inclusion into the analysis. We then selected 100 low-grade PC cases (Gleason = 6 (3+3)) and 100 high-grade PC cases (Gleason = 7 (4+3), 8,9,10). Gleason 3+4 PCs were omitted to better separate the low-grade from high-grade cancer groups. We then identified 160 biopsy-negative controls for analysis. To allow us to better control for known age differences between these diagnostic groups, cancer cases and

controls groups were randomly selected from the pool of available patients such that PC cases and controls were frequency-matched by 5-year age categories according to the distribution of patients in the HGPIN group. This created comparable age distributions across the diagnostic groups, but we were forced to relax the age categorization within the high-grade PC group because there were too few of these high-grade PC cases in the youngest age category. Leptin, adiponectin, estradiol, and C-peptide were assayed in the Vanderbilt Endocrinology Laboratory by radioimmunoassay (Luminex, Corp., Austin, TX). Power calculations assuming an Type I error = 0.05 and Type II error = 0.20 suggest a simple t-test would detect differences in leptin, C-peptide, adiponectin, and estradiol of 1.6 ng/ml, 1.4 ng/ml, 4.7 μg/ml, and 7.0 ng/ml, respectively, between 50 cases and 50 controls typical within subset analyses. All assays were performed in accordance with manufacturer protocols. We excluded 6 estradiol values with assay failure or levels below the minimum detection limit. Intra-assay CVs for leptin, adiponectin, estradiol, and C-peptide were 8.0%, 6.0%, 1.5%, and 8.6%, respectively.

2.6 Statistical analysis

For analysis, we excluded participants taking steroid reductase inhibitors finasteride or dutasteride, leaving 457 participants. Chi-square and Kruskal-Wallis tests were used for univariate comparisons of study characteristics between cases and controls. Spearman correlation coefficients and Wilcoxon Rank Sum tests were used to compare body size and biomarker measures.

Case-control differences in BMI, leptin, and other body size and blood biomarker indices were evaluated in a linear model that allowed us to adjust for factors identified as significantly different between diagnostic groups, including age, alpha-blocker use, treatment for diabetes, prostate volume, and number of cores at biopsy. Additional analyses included other considered variables but results were not substantively affected. Leptin and C-peptide levels were natural log transformed prior to analysis to normalize these distributions, and geometric means and standard errors are reported. A two-sided p-value of 0.05 or less was considered statistically significant. Multivariable logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) summarizing the association between PC and HGPIN with obesity measures categorized using BMI ≥ 30 or the median value of the control series. Interaction between obesity measures and prostate volume were estimated by the significance of the respective cross-product term in a model that included both main effects. After observing a significant cross-product interaction between BMI and prostate volume, we repeated all analyses stratified by a prostate volume of 40 ml or more, as this was approximately the median value (median = 42 ml) in our study.

We used a risk-difference approach to assess the mediating role of obesity biomarkers on associations between measured body size and PC. For example, the OR for the association between BMI and prostate cancer is calculated, then the change in this OR is evaluated after including leptin or another biomarker to the model. The extent to which the original OR for the association between BMI and PC shifts toward 1.0 after including leptin provides an estimate of the mediating role of leptin on the BMI-PC association.

3. Results

Participants ranged in age from 50 to 79 years (Table 1). Approximately 35% of controls and 40% of high-grade PC cases had a BMI greater than 30, and most study participants self-described as non-Hispanic white. Diagnostic groups significantly differed with regard to PSA level, prostate volume, being treated for diabetes, and use of alpha-blockers for the treatment of lower urinary tract symptoms.

Tables 2 and 3 summarize the relationships between body size measures and obesity biomarkers. Leptin, C-peptide, and estradiol were significantly higher, while adiponectin was lower, with a higher BMI and WC. Leptin and C-peptide were also significantly higher with a higher WHR. The correlations between leptin with BMI, WC, and WHR were moderately strong across all diagnostic groups (Table III). C-peptide correlations with obesity measures were somewhat weaker and not always significant within PC cases, while estradiol and adiponectin held weaker and less consistent correlations with body size. Biomarkers of obesity were not consistently correlated with height or PSA levels. However, prostate volume was positively correlated with leptin and C-peptide among controls. Furthermore, there was a significant but inverse correlation between C-peptide and prostate volume within high-grade PC cases.

Table IV summarizes multivariable linear regression analyses estimated adjusted mean body size and biomarker levels across controls, HGPIN cases, and PC cases. There was a significant interaction between prostate volume and diagnostic group in predicting BMI (p-interaction = 0.039), suggesting the ability to identify differences in BMI between diagnostic groups was dependent on prostate volume. Among men without prostate enlargement, BMI increased across controls, HGPIN, low-grade PC, and high-grade PC such that high-grade PC cases had a significantly higher BMI than controls (p=0.02). In contrast, BMI did not significantly differ across diagnostic groups within men experiencing prostate enlargement. Similarly, an association between leptin and PC was dependent on prostate volume (p-interaction = 0.010), such that significantly higher leptin levels were found with high-grade PC (p=0.01) and HGPIN cases (p=0.03) compared to controls in the absence of prostate enlargement. In contrast, high-grade PC cases had significantly lower leptin levels than controls (p=0.03) within men with prostate enlargement. Although formal tests of interaction between diagnosis and prostate volume in predicting C-peptide (p-interaction=0.088) and WC (p-interaction=0.053) were marginal, we saw a similar pattern in that high-grade PC cases had significantly higher C-peptide (p=0.04) and WC (p=0.01) than controls when restricting the analysis to men without prostate enlargement.

Logistic regression analyses investigating the association between obesity levels and HGPIN and PC were similarly dependent on prostate volume (Table V). BMI greater than 30 was significantly associated with an increased risk of high-grade PC among men without prostate enlargement (OR=4.88 (1.78, 13.3)), but not among men with prostate enlargement (OR=0.48 (0.20, 1.17), BMI × prostate volume interaction: $p < 0.001$). A higher leptin level also was significantly associated with high-grade PC among men without prostate enlargement (OR=3.00 (1.16, 7.73)), but not among men with prostate enlargement (OR=0.56 (0.26, 1.21), leptin × prostate volume interaction: p=0.005). Leptin was also associated with HGPIN among men with a smaller prostate volume (OR=4.92 (1.72, 14.0), leptin × prostate volume interaction: $p = 0.002$). An association between WHR and high-grade PC was similarly restricted to men without prostate enlargement. Similar to leptin, interactions between prostate volume and C-peptide levels were also significant for HGPIN (p-interaction = 0.027) and high-grade PC (p-interaction = 0.011), while marginal for low-grade PC (p-interaction=0.051). However, C-peptide was the only obesity measure significantly associated with low-grade PC (OR=2.53 (1.02, 6.27)). In contrast, adiponectin and estradiol were not associated with PC or HGPIN. Additional control for race/ethnicity, family history of PC, treatment for CVD (e.g., anti-hypertensives, calcium channel blockers, etc.), or treatment for hyperlipidemia (e.g., statins, niacin, etc.) did not affect results (not shown).

Restricting to men without prostate enlargement, we evaluated the mediating effect of leptin and other obesity-related biomarkers on the significant associations found between high-grade PC and BMI or WHR (Table VI). The association between BMI and high-grade PC

was reduced approximately 15% with control for leptin. However, BMI remained significantly associated with high-grade PC regardless of the biomarker included in the model. Similar to the analysis of BMI, the association between WHR and high-grade PC shifted by less than 10% with addition of leptin or another biomarker.

4. Discussion

Multiple recent reviews and meta-analyses summarize the contrasting associations between obesity and prostate cancer [8, 12, 16, 32–34]. Though at this point there is strong evidence that obesity adversely affects PC prognosis, the possibility that obesity may have little impact, or indeed reduce the risk, of the most commonly diagnosed PC phenotypes has limited efforts to develop obesity-driven PC prevention strategies. This analysis suggests that detection bias related to prostate size may be obscuring a positive association between obesity and HGPIN, low-grade PC, and high-grade PC. To varying degrees, BMI, WC, WHR, leptin, and C-peptide were associated with increased PC or HGPIN risk when analyses were restricted to men without prostate enlargement. Several interactions between obesity, diagnosis, and prostate volume were statistically significant, and interestingly, BMI and other measures were somewhat protective for PC among those men found with prostate enlargement. Such results would be consistent with the hypothesis that obesity-driven prostate enlargement reduces prostate biopsy efficiency and the ability to detect PC.

Prostate enlargement is a common consequence of aging, and most men with an elevated PSA level who are referred for biopsy are diagnosed with a benign disease rather than PC. However, the impact of prostate size on PC detection was recently illustrated in the PCPT. The PCPT tested the efficacy of finasteride, a steroid reductase inhibitor blocking conversion of testosterone to dihydrotestosterone, in the chemoprevention of PC. Finasteride significantly reduced the diagnosis of low-grade PC, but the clinical utility of finasteride was questioned when investigators found that finasteride was also associated with increased risk of high-grade PC [24]. However, finasteride is known to reduce prostate size, by an average of 24% in the case of the PCPT. With a smaller prostate volume, each biopsy core represents a greater proportion of the total prostate gland, potentially increasing the likelihood of finding a small lesion that would otherwise be missed. Thus, rather than finasteride increasing the risk of high-grade PC, the conflicting effects of finasteride in the PCPT alternatively might be explained by a reduction in prostate volume with finasteride leading to the collection of cancer tissue from smaller lesions that might otherwise be missed, more cancer tissue per core to improve pathology review, or more accurate grading with more cancer tissue per core [35]. Indeed, the excess risk of high-grade PC associated with finasteride treatment in PCPT disappeared after controlling for the number of biopsy cores and prostate volume [36]. Though circumstantial overall, the PCPT provides a framework to consider the possibility that it is difficult to understand the effect of an agent on PC risk when that agent also affects prostate size.

Obesity could be considered the opposite of finasteride, in that obesity is a consistent risk factor for prostate enlargement and benign prostatic hyperplasia [37, 38]. For example, BMI and WHR were associated with lower urinary tract symptom severity in the PCPT [37], while an increasing trend in WC was significantly associated with surgery to relieve symptoms of BPH in the Health Professionals Follow-up Study [38]. Similarly, BMI was associated with a larger prostate volume in the Olmstead County and Baltimore Longitudinal Study of Aging cohorts [39, 40], while obesity-related diseases such as coronary heart disease and diabetes are also associated with prostate enlargement or BPH in the Massachusetts Male Aging Study [41]. We have previously reported the significant positive associations between BMI and prostate size in the NMHS [42, 43]. In this context, our results suggest that it is more difficult to detect an association between obesity and PC in

the presence of obesity-driven prostate enlargement. We saw an obesity-PC association only when we restricted to men without prostate enlargement. In contrast, obesity was not strongly associated, or perhaps somewhat protective, for PC among obese men with prostate enlargement. This was independent of the number of biopsy cores collected. In this situation, we speculate that obesity-driven prostate enlargement may be reducing the ability to identify prostate cancer at biopsy, obscuring any association or lending the appearance of a protective association between obesity and PC risk. Inconsistent associations across past studies showing an increased risk for high-grade PC but decreased risk for low-grade PC may be an artifact of the loss of biopsy efficiency derived from obesity-driven prostate enlargement.

Restricting analyses to men without prostate enlargement and thus reducing this potential detection bias, we found BMI and WHR were significantly associated with high-grade PC. WC was also significantly higher among high-grade PC cases. These obesity measures are simple to calculate in large studies but are also strongly correlated (r=0.60 to 0.90) and provide little information on possible mediating pathways. Indeed, BMI in men may be just as strongly correlated with total fat-free mass (e.g., muscle, bone) as with fat mass [44, 45] and interpreting BMI as only an estimate of body adiposity may be misleading [46]. Waist circumference (WC) and waist-hip ratio (WHR) better approximate centralized adiposity, but do not directly measure visceral adiposity involved in abnormal glucose-insulin metabolism and dyslipidemia that occurs with aging [47]. WC or WHR have been associated with PC risk but the role of centralized adiposity in HGPIN, early PC, or advanced PC independent of BMI or the correlates of BMI has been unclear [8, 9]. In this context, we investigated four biomarkers related to obesity that may signal the aspects of adiposity most relevant to PC.

Leptin was associated with all PC outcomes in the absence of prostate enlargement, with significant associations for high-grade PC and HGPIN, and a non-significant increased risk for low-grade PC. Other markers were not significantly associated with PC, although the marginally significant association between C-peptide and high-grade PC may have been limited by our sample size. Leptin is released in proportion to white adipose tissue and acts on the central nervous system to regulate energy balance and appetite. However, leptin also modulates immune cell activity, oxidative stress, and promotes angiogenesis, and leptin may also act directly on prostate cells to affect steroid activity, cell cycle regulation, and insulin sensitivity [16, 48]. Obese subjects also may express higher than expected leptin levels as cells lose leptin sensitivity with sustained leptin exposure, perhaps accelerating systemic or direct effects on prostate carcinogenesis beyond what might be observed when evaluating BMI alone. Our data illustrate the limitations of assessing a single obesity measure, as BMI and WHR were significantly associated with PC and control for leptin had only a modest impact on their associations with high-grade PC. The literature finds a decidedly mixed relationship between leptin and PC risk [49–51]. Our inability to account for the effects of BMI through leptin may derive from the limitations of a single blood measure of leptin. However, our data suggest the association between BMI and PC is not mediated by leptin, and that the effect of BMI on PC risk may be mediated by effects on androgens, IGFs, or something other than the amount of adipose tissue in the body. Similarly, we found C-peptide levels, reflecting insulin release, explained only a minor component of the significant association between WHR and high-grade PC. Certainly inflammation, oxidative stress, androgens, and other pathways correlated with adiposity may be involved.

Strengths of this investigation include the ability to control for differences in prostate cancer screening and diagnostic protocols potentially associated with obesity. BMI is associated with lower blood PSA levels and a larger prostate size, such that potential stage-specific associations between obesity and prostate cancer may be an artifact of factors that influence

the ability to detect prostate cancer[42]. However, the study design controls for selective biopsy referral possibly related to the effects of body size on PSA, and therefore control for PSA differences in this analysis was unnecessary because all participants were biopsied. Indeed, we find little relationship between obesity and PSA levels among men with PSA sufficient for biopsy referral. We also controlled for factors that differed between groups, including prostate size, number of biopsy cores, and treatment for LUTS and diabetes. Inclusion of men without cancer or HGPIN at biopsy reduces a potential bias to the null associated with inclusion of latent or indolent disease in the control group, and similar data on medication history, screening history, and prostate size are available for analyses. Body size was measured by trained staff and prior to diagnosis to prevent any bias related to the knowledge of diagnosis on data collection, patient reporting, or treatment effects [52]. Our results were not affected by the time between blood collection and the participant's last meal or last liquid (not shown). We included a novel analysis of HGPIN to consider the potential that obesity related biomarkers impact an early phase in prostate carcinogenesis.

A limitation of this analysis is the cross-sectional design. Although reverse causality cannot be excluded, it is unclear how undiagnosed PC may affect BMI, WC, or WHR. All data, including body size and blood collection, were obtained prior to the participant's knowledge of their cancer status, excluding the possibility of behavioral or other changes in response to the knowledge of cancer status. The majority of participants were non-Hispanic white, and therefore our results may not generalize to other race/ethnicities. Our data suggested that the effects of BMI on PC risk are not related strongly to leptin, C-peptide, estradiol or adiponectin, but we cannot say with any certainty what alternative pathway(s) might be involved.

In summary, prostate size substantially modified the association of prostate cancer with BMI and leptin, and perhaps also C-peptide. Among men without prostate enlargement and thus less susceptible to a detection bias, leptin levels were significantly associated with HGPIN and high-grade PC. However, BMI remained significantly associated with high-grade PC after controlling for leptin, suggesting the involvement of other pathways. Since prostate enlargement and PC are both conditions associated with aging and obesity, these data argue for greater care separating the effects of obesity and prostate size in order to identify the underlying relationship between obesity and PC.

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Table I

Description of Study Participants (n=457)

		Control (n=137)		HGPIN (n=127)		Low-grade (n=95)		High-grade (n=98)		
		n	%	n	%	n	%	n	%	p**
Age	50–59 yrs	27	19.7%	30	23.6%	16	16.0%	12	12.2%	0.37
	60–69 yrs	52	38.0%	53	41.7%	41	43.6%	47	47.9%	
	70–79 yrs	58	42.3%	44	34.6%	38	40.4%	39	39.8%	
Race/ethnicity*	NHW	122	89.1%	112	88.2%	84	88.4%	87	88.8%	0.71
	other	15	11.0%	15	11.8%	11	11.7%	11	11.2%	
PSA (ng/ml)	less than 4.0	43	31.9%	13	10.4%	13	13.8%	4	4.1%	<0.01
	4.0 – 5.9	49	36.3%	54	43.2%	43	45.7%	32	32.7%	
	6.0 – 7.9	21	15.6%	26	20.8%	14	14.9%	15	15.3%	
	8.0 – 9.9	9	6.7%	14	11.2%	13	13.8%	8	8.1%	
	10.0 or more	13	9.6%	18	14.4%	11	11.7%	39	39.8%	
Prostate	less than 40.0	41	31.1%	49	39.5%	53	57.0%	50	52.6%	<0.01
Volume (ml)	40.0 or more	91	68.9%	75	60.5%	40	43.0%	45	47.4%	
Cores at	11 or less	55	40.2%	29	22.8%	29	30.5%	33	33.7%	<0.01
biopsy	12	53	38.7%	59	46.5%	53	55.8%	45	45.9%	
	13 or more	29	21.1%	39	30.7%	13	13.7%	20	20.4%	
BMI	less than 30	89	65.0%	87	68.5%	65	68.4%	59	60.2%	0.55
	30 or more	48	35.0%	40	31.5%	30	31.6%	39	39.8%	
Waist	less than 104.1	56	40.9%	58	45.7%	41	43.6%	40	41.2%	0.86
Circumference (cm)	104.1 or more	81	59.1%	69	54.3%	53	56.4%	57	58.8%	
WHR	less than 1.01	68	49.6%	67	52.8%	37	39.4%	38	39.6%	0.09
	1.01 or more	69	50.4%	60	47.2%	57	60.6%	58	60.4%	
Height (cm)	less than 175.3	65	47.5%	52	41.6%	51	53.7%	40	42.1%	
	175.3 or more	72	52.5%	73	58.4%	44	46.3%	55	57.9%	0.27
α-blockers use***	Yes	46	33.6%	27	21.3%	23	24.2	14	14.3%	0.01
	No	91	66.4%	100	78.7%	72	75.8%	84	85.7%	
Diabetes Tx***	Yes	24	17.5%	10	7.9%	13	13.7%	28	28.6%	<0.01

		Control (n=137)		HGPIN (n=127)		Low-grade (n=95)		High-grade (n=98)		
		n	%	n	%	n	%	n	%	p**
CVD Tx***	No	113	82.5%	117	92.1%	82	86.3%	70	71.4%	
	Yes	84	61.3%	72	56.7%	59	62.1%	62	63.3%	0.75
Hypercholesterolemia Tx***	No	53	38.7%	55	43.3%	36	37.9%	36	36.7%	
	Yes	58	42.3%	48	37.8%	37	39.0%	44	44.9%	0.71
	No	79	57.7%	79	62.2%	58	61.0%	54	55.1%	

* NHW = non-Hispanic White, 'other' includes 50 African Americans, 1 Hispanic White, and 1 Asian.

** p-value from chi-square test for homogeneity in distribution across diagnostic groups;

*** Determined by medical chart review.

Total may be less than 457 due to missing values in medical record.

Table II

Obesity biomarker levels across categories of BMI, waist circumference (WC), waist-hip ratio (WHR), and height.

			Leptin (ng/ml)			C-peptide(ng/ml)			Adiponectin (ug/ml)			Estradiol (ng/ml)		
			Median	**25th**	**75th**	**Median**	**25th**	**75th**	**Median**	**25th**	**75th**	**Median**	**25th**	**75th**
BMI	less than 30		6.92	4.17	10.84	2.03	1.43	3.00	21.1	15.78	26.84	30.09	24.05	39.87
	30 or more		18.50	10.50	25.59	2.93	2.05	3.89	18.88	14.34	22.63	35.12	26.84	46.17
		p		<0.001			<0.001			<0.001			<0.001	
WC (cm)	less than 104.1		5.91	3.64	8.84	1.76	1.23	2.68	21.78	15.74	27.06	29.44	24.11	39.42
	104.1 or more		14.41	8.28	25.38	2.83	1.89	3.77	19.23	14.78	23.06	33.89	25.76	42.68
		p		<0.001			<0.001			0.008			0.017	
WHR	less than 1.01		7.30	4.06	11.34	1.86	1.32	2.88	20.82	15.74	26.15	31.85	24.60	40.23
	1.01 or more		12.42	6.99	23.27	2.68	1.77	3.82	19.60	14.63	23.51	33.10	25.44	42.04
		p		<0.001			<0.001			0.065			0.205	
Height (cm)	less than 175.3		8.88	5.70	17.83	2.35	1.60	3.45	20.16	15.09	25.14	30.21	23.88	41.02
	175.3 or more		8.93	5.06	17.43	2.23	1.49	3.25	19.71	15.46	25.02	33.07	25.51	41.43
		p		0.904			0.183			0.730			0.156	

P: wilcoxon rank sums test

Table III

Spearman Correlation Coefficients between Blood Biomarkers with BMI, Waist Circumference (WC), Waist-Hip Ratio (WHR), Height, PSA, and Prostate Volume.

		leptin	C-peptide	adiponectin	estradiol
BMI	Controls	0.63 ***	0.43 ***	−0.18 *	0.23 **
	HGPIN	0.62 ***	0.40 ***	−0.16	0.14
	low-grade PC	0.63 ***	0.13	−0.39 ***	0.27 **
	high-grade PC	0.73 ***	0.33 ***	−0.14	0.12
WC	Controls	0.68 ***	0.55 ***	−0.11	0.19 *
	HGPIN	0.62 ***	0.37 ***	−0.16	0.10
	low-grade PC	0.67 ***	0.18	−0.31 **	0.19
	high-grade PC	0.74 ***	0.32 **	−0.06	0.15
WHR	Controls	0.32 ***	0.46 ***	−0.01	0.06
	HGPIN	0.49 ***	0.27 **	−0.15	0.03
	low-grade PC	0.55 ***	0.23 *	−0.28 **	0.06
	high-grade PC	0.35 ***	0.16	−0.09	0.09
Height	Controls	−0.02	0.02	0.05	0.10
	HGPIN	−0.15	−0.16	−0.18 *	0.04
	low-grade PC	0.07	−0.06	−0.04	0.01
	high-grade PC	−0.03	−0.27 **	−0.08	0.04
PSA	Controls	0.00	0.11	0.07	−0.09
	HGPIN	0.06	−0.08	0.01	−0.05
	low-grade PC	0.23 *	0.06	0.01	0.14
	high-grade PC	−0.02	−0.15	0.19	−0.01
Prostate	Controls	0.23 **	0.28 **	0.13	−0.03
Volume	HGPIN	0.03	−0.08	0.06	0.07
	low-grade PC	0.19	−0.03	−0.08	−0.05
	high-grade PC	−0.19	−0.21 *	−0.05	−0.05

* p<0.05,

** p<0.01,
*** p<0.001

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Table IV

Adjusted body size and obesity biomarker levels across controls, HGPIN cases, and PC cases; with additional stratification by prostate volume.

		Controls		HGPIN		low-grade PC		high-grade PC		p$	p-int
		mean	se	mean	se	mean	se	mean	se		
BMI (kg/m2)	All[!$]	29.3	0.43	29.1	0.47	29.5	0.52	29.8	0.49	0.71	
	Volume ≤ 40	28.5	0.77	28.9	0.79	29.2	0.75	30.7**	0.74	0.11	0.039
	Volume >40	30.0	0.51	29.6	0.60	30.0	0.73	29.0	0.69	0.61	
WC (cm)	All	106.5	1.15	106.7	1.26	107.6	1.38	109.6	1.33	0.28	
	Volume ≤ 40	104.9	1.99	107.2	2.03	106.2	1.93	110.5**	1.92	0.13	0.053
	Volume >40	108.3	1.42	106.9	1.67	109.2	2.04	108.9	1.92	0.69	
WHR	All	1.03	0.01	1.03	0.01	1.03	0.01	1.04	0.01	0.25	
	Volume ≤ 40	1.01	0.01	1.04	0.01	1.03	0.01	1.03	0.01	0.36	0.059
	Volume >40	1.03	0.01	1.02	0.01	1.04	0.01	1.05	0.01	0.23	
Height (cm)	All	174.4	0.61	174.6	0.67	173.9	0.73	175.7	0.70	0.42	
	Volume ≤ 40	175.0	0.98	174.2	1.00	173.1	0.95	174.8	0.94	0.35	0.161
	Volume >40	174.4	0.81	175.1	0.94	174.7	1.15	176.5	1.09	0.37	
Leptin (ng/ml)	All	10.22	1.09	9.83	1.10	11.17	1.11	10.13	1.11	0.77	
	Volume ≤ 40	8.46	1.17	12.38**	1.17	10.51	1.16	13.27**	1.16	0.09	0.010
	Volume >40	11.28	1.11	8.75	1.14	12.09	1.17	7.87**	1.16	0.03	
C-peptide (ng/ml)	All	2.28	1.07	2.31	1.07	2.25	1.08	2.44	1.08	0.85	
	Volume ≤ 40	2.00	1.12	2.62	1.12	2.42	1.11	2.67**	1.11	0.14	0.088
	Volume >40	2.36	1.09	2.09	1.10	2.06	1.12	2.19	1.12	0.59	
Adiponectin (μg/ml)	All	19.84	0.79	20.79	0.87	19.82	0.96	18.62	0.92	0.29	
	Volume ≤ 40	19.04	1.44	19.97	1.47	20.03	1.41	19.58	1.39	0.94	0.577
	Volume >40	20.30	2.56	21.47	3.00	19.53	3.82	17.64	3.58	0.07	
Estradiol (ng/ml)	All	33.3	1.21	31.9	1.33	35.0	1.47	33.0	1.40	0.33	
	Volume ≤ 40	32.8	2.03	32.0	2.07	35.0	1.97	34.4	1.96	0.59	0.719
	Volume >40	33.7	4.72	31.8	6.24	35.0	9.58	31.6	8.08	0.48	

[*] All subjects analyzed, with mean obesity values adjusted for age, alpha-blocker use, treatment for diabetes, prostate volume, and number of cores at biopsy. Analyses were repeated within prostate volume categories, adjusted for age, alpha-blocker use, treatment for diabetes, and number of cores at biopsy. Leptin and C-peptide levels were natural log transformed, and geometric mean values are reported.

$ p value for the diagnostic group covariate representing a global test of differences in means across diagnostic groups.

** Significantly different from Controls at p≤0.05. p-int is p-value for test of interaction between group and prostate volume in predicting obesity measure.

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Table V

Logistic regression analysis providing odds ratios (OR) and 95% confidence intervals (95% CI) for association between obesity categories with HGPIN or prostate cancer, and stratified by prostate volume.

		HGPIN			low-grade PC			high-grade PC		
		OR	**95% CI**	**p**	**OR**	**95% CI**	**p**	**OR**	**95% CI**	**p**
BMI	All	1.01	0.58, 1.76	0.97	1.01	0.55, 1.85	0.98	1.30	0.72, 2.34	0.38
(>30 kg/m vs. ≤30 kg/m)	Volume ≤ 40	1.69	0.59, 4.87	0.33	1.63	0.61, 4.36	0.34	4.88	1.78, 13.3	<0.01
	Volume >40	0.95	0.48, 1.91	0.89	0.69	0.30, 1.59	0.38	0.48	0.20, 1.17	0.11
Waist	All	0.99	0.58, 1.68	0.96	1.06	0.59, 1.90	0.85	1.02	0.57, 1.82	0.96
(> 104.1 cm vs. ≤104.1 cm)	Volume ≤ 40	1.41	0.57 3.47	0.46	1.20	0.49 2.95	0.79	1.59	0.66, 3.84	0.30
	Volume >40	0.90	0.45, 1.78	0.76	1.06	0.47, 2.39	0.89	0.76	0.34, 1.71	0.51
WHR	All	0.95	0.57, 1.60	0.85	1.60	0.91, 2.84	0.10	1.66	0.94, 2.95	0.08
(>1.01 vs. ≤1.01)	Volume ≤ 40	1.75	0.70, 4.37	0.22	2.22	0.91, 5.42	0.08	2.52	1.02, 6.26	0.05
	Volume >40	0.68	0.35, 1.31	0.25	1.36	0.62, 2.97	0.44	1.34	0.62, 2.91	0.45
Height	All	1.24	0.74, 2.10	0.42	0.88	0.50, 1.54	0.66	1.62	0.90, 2.90	0.11
(> 175.3 cm vs. ≤175.3 cm)	Volume ≤ 40	1.14	0.47, 2.74	0.78	0.56	0.23, 1.34	0.19	1.24	0.50, 3.05	0.64
	Volume >40	1.27	0.65, 2.47	0.48	1.11	0.51, 2.40	0.79	1.63	0.75, 3.61	0.21
Leptin	All	1.26	0.75, 2.12	0.36	1.88	1.05, 3.37	0.03	1.11	0.63, 1.96	0.71
(>8.49 ng/ml vs. ≤8.49 ng/ml)	Volume ≤ 40	4.92	1.72, 14.0	<0.01	1.90	0.74, 4.88	0.18	3.00	1.16, 7.73	0.02
	Volume >40	0.71	0.37, 1.36	0.30	1.78	0.79, 4.07	0.17	0.56	0.26, 1.21	0.14
C-peptide	All	0.85	0.51, 1.43	0.55	1.33	0.74, 2.38	0.33	0.98	0.55, 1.74	0.94
(>2.34 ng/ml vs. ≤2.34 ng/ml)	Volume ≤ 40	2.26	0.88, 5.81	0.09	2.53	1.02, 6.27	0.05	2.45	0.99, 6.06	0.05
	Volume >40	0.59	0.31, 1.13	0.11	0.82	0.37, 1.82	0.63	0.54	0.24, 1.20	0.13
Adiponectin	All	0.63	0.37, 1.09	0.10	1.46	0.80, 2.65	0.22	0.96	0.53, 1.76	0.90
(<20.15 ng/ml vs.≥20.15 ng/ml)	Volume ≤ 40	0.60	0.24, 1.53	0.29	1.17	0.45, 3.06	0.75	0.63	0.23, 1.68	0.33
	Volume >40	0.68	0.34, 1.37	0.28	1.51	0.66, 3.45	0.33	1.32	0.60, 2.94	0.49
Estradiol	All	0.73	0.43, 1.24	0.25	1.05	0.59, 1.89	0.86	0.80	0.44, 1.45	0.46
(> 32.2 ng/ml vs. ≤32.2 ng/m)	Volume ≤ 40	0.44	0.17, 1.16	0.10	1.26	0.50, 3.15	0.63	1.11	0.43, 2.86	0.83
	Volume >40	0.89	0.46, 1.71	0.73	1.08	0.49, 2.38	0.85	0.64	0.28, 1.4660	0.29

Obesity measures categorized at median value of control group distribution, with the exception of WHO criteria for BMI. All analyses adjusted for age, alpha-blocker use, treatment for diabetes, and number of cores collected at biopsy. Analyses of all participants also adjusted for prostate volume.

Table VI

Risk Difference Analysis of BMI or WHR and high-grade PC

Body Size Measure	Model Covariate	$OR_{(body\ size)}$	95% $CI_{(body\ size)}$	$P_{(body\ size)}$	$P_{(biomarker)}$
BMI (>30 kg/m vs. ≤30 kg/m)	base model *	4.88	1.79, 13.3	0.002	----
	+ leptin	4.13	1.23, 13.8	0.022	0.633
	+ c-peptide	4.23	1.52, 11.8	0.006	0.234
	+ adiponectin	5.20	1.86, 14.6	0.002	0.214
	+ estradiol	4.58	1.66, 12.6	0.003	0.731
	+ all **	4.07	1.14, 14.5	0.030	---
WHR (>1.01 vs. ≤1.01)	base model	2.52	1.02, 6.23	0.046	-----
	+ leptin	2.45	0.96, 6.29	0.062	0.022
	+ c-peptide	2.23	0.88, 5.68	0.090	0.079
	+ adiponectin	2.81	1.11, 7.12	0.030	0.228
	+ estradiol	2.39	0.96, 5.96	0.061	0.702
	+ all	2.41	0.91, 6.41	0.078	----

Analysis of obesity and high-grade PC restricted to men without prostate enlargement (prostate volume < 40 ml).

* base model investigating the association between BMI/WHR with high-grade PC included age, alpha blocker use, treatment for diabetes, and number of cores at biopsy. Leptin or other listed biomarkers were then added individually to the base model, and the adjusted OR, 95% CI, and p-value for each body size measure (BMI/WHR) is reported. The p-value for the biomarker within the model is also listed. A change in the OR from the base model would suggest that biomarker is a mediator.

** model includes all biomarkers together with the base model.