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Obesity is a Significant Risk Factor for Prostate Cancer at the time of Biopsy

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Abstract

Background—Studies suggest obesity is associated with decreased prostate cancer risk. We hypothesized obesity is biologically associated with increased risk, though this is obscured due to hemodilution of PSA and larger prostate size.

Methods—Retrospective study of 441 consecutive men undergoing prostate biopsy between 1999 and 2003 at two equal access centers. The association between obesity (body mass index ≥30 kg/m^2) and positive biopsy and Gleason ≥4+3 were estimated using logistic regression analysis adjusting for multiple clinical characteristics.

Results—123 men (28%) were obese and 149 men (34%) had cancer. Median PSA and age were 5.7 ng/ml and 63.9 years. Obese men had significantly lower PSA concentrations (p=0.02) and larger prostate volumes (p=0.04). Obesity was not significantly related to age (p=0.19) or race (p=0.37). On univariate analysis, obesity was not associated with prostate cancer risk (OR 1.13, 95% CI 0.73–1.75, p=0.58). However, after adjusting for multiple clinical characteristics, obesity was associated with significantly increased prostate cancer risk (OR 1.98, 95% CI 1.17–3.32, p=0.01). After multivariable adjustment, there was no significant association between obesity and high-grade disease (p=0.18).

Conclusions—Without adjustment for clinical characteristics, obesity was not significantly associated with prostate cancer risk in this equal access clinic-based population. However, after adjusting for the lower PSA levels and the larger prostate size, obesity was associated with a 98% increased prostate cancer risk. These findings support the fact current prostate cancer screening practices may be biased against obese men.

Keywords

Body mass index; obesity; prostate cancer; prostate volume; PSA

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INTRODUCTION

Obesity is a major public health concern. Regarding prostate cancer, multiple prospective cohort studies found obesity was associated with increased risk of prostate cancer death.[1,2] However, three large prospective cohort studies in the United States all found obesity was associated with a reduced risk of prostate cancer diagnosis.[3–5] One possible explanation for the lower risk of prostate cancer diagnosis among obese men is that cancers may be more difficult to detect. For example, multiple studies found obese men with[6] and without prostate cancer[7–12] have lower PSA values than normal weight men, possibly related to hemodilution from greater plasma volume in obese men.[6] Consequently, obese men are less likely to have an elevated PSA, less likely to undergo a biopsy, and thus less likely to be diagnosed with prostate cancer. Moreover, obese men have larger sized prostates[13,14] making cancer detection at biopsy more difficult. Indeed, we previously noted that while obese men in general undergoing prostate biopsy were less likely to have cancer, after adjustment for differences in PSA and prostate size among other factors, obese men were actually more likely to have cancer and were more likely to have higher grade tumors.[15]

We hypothesized obese men are at greater risk of prostate cancer development, but technical factors related to cancer detection such as lower PSA values and larger prostate sizes make detection of these cancers more difficult. To test this hypothesis, we examined the association between obesity, PSA, prostate size, and prostate cancer risk among a multi-racial population undergoing prostate needle biopsy within an equal access health care system.

MATERIALS AND METHODS

Study population and assessment of clinical and pathological variables

A total of 724 patients referred due to abnormal digital rectal examination (DRE) and/or elevated PSA underwent an initial prostate needle biopsy between January 1, 1999 and March 30, 2003 at the Sepulveda or West Los Angeles Veteran's Affairs Medical Center. Being equal access medical centers, these centers provide access to care regardless of race or insurance status. After obtaining Internal Review Board approval, clinical information was retrospectively abstracted including age, height, and weight measured prior to biopsy and nearly always within 2 months of the biopsy, race, PSA concentration, DRE findings, and prostate volume estimated by transrectal ultrasound. Pathological information included the presence or absence of cancer and the Gleason sum. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Patients were excluded if they had missing data for pre-biopsy PSA (n=1), DRE findings (n=3), race (n=5), BMI (n=2), or TRUS volume (n=254). Men with missing TRUS data had higher PSA values (p=0.03) and were nearly exclusively biopsied at one of the two centers. However, the magnitude of the association between obesity and prostate cancer risk (the primary end-point of this study) after adjusting for age and PSA was little changed when men with missing TRUS volumes were excluded or included. Given the presumed importance of TRUS volumes as contributing to missing prostate cancers in obese men, we limited our analysis to men with TRUS volume data available. Patients were excluded if <6 biopsy cores or an unknown number of cores were obtained (n=18), resulting in a study population of 441.

Statistical analysis

We initially categorized BMI (kg/m^2) as: <25 for normal weight, ≥25 to <30 for overweight, ≥30 for obese. As the cancer risk was similar between normal weight and overweight men, these groups were combined and BMI was ultimately examined as a dichotomous variable

of obese vs. non-obese. We also examined BMI as a continuous variable. Tests for associations between categorized BMI and clinical variables were done using ranksum for continuous variables and chi-squared for categorical variables.

Cancer risk was assessed using logistic regression. We performed crude, age-adjusted, and multivariate analysis adjusting for age (continuous), race (black, nonblack-nonwhite vs. white), center (Sepulveda vs. West Los Angeles) and factors predicted to influence the detectability of an existent tumor including PSA (continuous), DRE findings (abnormal vs. normal) and prostate volume (continuous). Among all men, we used logistic and linear regression to examine the association between obesity and high-grade biopsy Gleason sum (≥4+3 vs. 3+4 or lower or no cancer) and percent of cores positive, respectively. Because the data for PSA concentration and prostate volume were not normally distributed, we examined the data after logarithmic transformation. All statistical analyses were performed using STATA 9.2 (Stata Corp., College Station, TX).

RESULTS

Mean ± SD and median BMI were 27.9 ± 5.0 kg/m^2 and 27.5 kg/m^2, respectively. Obese men had lower PSA concentrations and larger prostate volumes than non-obese men (table 1). Overall 149 (34%) men had prostate cancer on biopsy, which was Gleason 2–6 in 68 (46%), 3+4 in 43 (29%) and ≥4+3 in 38 (26%).

On both crude (OR=1.13, p=0.58) and age-adjusted analysis (OR=1.22, p=0.37), obesity was not significantly related to prostate cancer diagnosis (table 2). However, after adjustment for multiple clinical characteristics including PSA concentration and prostate volume, obesity was associated with a significantly higher odds of being diagnosed with prostate cancer on biopsy (OR=1.98, p=0.01, table 2). Similar results were seen when BMI was coded as a continuous variable. Given that on univariate analysis obesity was not related to prostate cancer risk, but was after multivariate adjustment, we assessed which clinical covariate had the greatest influence on modifying the association between BMI and prostate cancer by adding each covariate to the age-adjusted model one at a time. Adding either prostate volume or PSA to the model generated the largest shifts in odds ratio for BMI, with PSA creating a larger shift than prostate volume. This indicates that both PSA and prostate volume were likely the major contributors to negating the positive association between BMI and prostate cancer.

As men with very high PSA values were extremely likely to have cancer, we evaluated whether these patients influenced our results. When analyses were restricted to men with a PSA <30, <20, or <10 ng/ml, the findings remained unchanged in that obesity was not significantly related to prostate cancer on crude or age-adjusted analysis, but was significantly related to cancer on multivariate analysis (data not shown).

Among all men, there was no significant association between obesity and high-grade disease on biopsy (≥4+3) after crude, age-adjusted, or multivariate adjusted analysis, though there was a suggestion of more high-grade disease after multivariate analysis (table 2). Using alternate definitions of high-grade (≥7 or ≥8) disease or restricting analyses to men with a PSA <30, <20, or <10 ng/ml did not materially change these results (data not shown). Among all men, obesity was not significantly related to the number of cores positive after crude or age-adjusted analysis (data not shown). However, after multivariate adjustment, obesity (p=0.09) and higher continuously coded BMI (p=0.02) were related to more cores positive. When analyses were restricted to men with cancer, obesity and BMI were not significantly related to cores positive even after multivariate analysis (data not shown).

DISCUSSION

We hypothesized obesity was biologically associated with an increased risk of prostate cancer development. We further hypothesized that factors related to prostate cancer detection, specifically the lower PSA values and larger prostate size, would obscure this association and reduce the risk of finding these cancers in obese men. To test this hypothesis we examined the association between obesity, PSA levels, prostate size, and prostate cancer risk. We found that obese men had lower PSA values and larger prostate volumes. On unadjusted analyses, there was no significant association between obesity and prostate cancer risk. However, after adjusting for clinical characteristics, including the lower PSA values and larger prostate sizes, obese men were significantly more likely to have cancer. Though there was a suggestion obese men were more likely to have high-grade prostate cancer, this association was not statistically significant. These findings add further support to a growing body of evidence suggesting that modern prostate cancer detection methods are biased against finding cancers in obese men.

In the United States, prostate biopsy is usually prompted by either an abnormal DRE finding suspicious for cancer or more often an elevated PSA blood test. Thus, any factor which affects PSA values can significantly alter our ability to detect prostate cancer. For example, it is well accepted that PSA values are reduce by at least a factor of 2 among men taking finasteride requiring PSA adjustment.[16] Age-specific reference ranges are commonly used to account for the increasing PSA values among older men.[17] More recently, mounting evidence has suggested that obesity is associated with lower PSA values,[7–12] possibly related to hemodilution from the large plasma volume in obese men.[6] The current study, albeit in a select population of men undergoing prostate biopsy also found obese men had lower PSA values. Indeed, the lower PSA values were the greatest contributor in the current study to obscuring the positive association between obesity and prostate cancer risk. To avoid this bias, we suggest that the PSA cut-offs for biopsy should be lower in obese men.

In the current study, and in line with prior studies,[13–15] obese men had larger sized prostates. The clinical implication is that at the time of biopsy it is more difficult to find the cancer, assuming a cancer exists. In a prior study using a larger multi-center series of men treated with radical prostatectomy, we estimated that the larger prostate size associated with obesity could result in up to 25% of all prostate cancers being missed in younger men.[18] In the current study, the larger prostate size was a key confounder in obscuring the association between obesity and prostate cancer risk. Likewise, in a prior study of men undergoing prostate biopsy at a VA hospital, we found that prostate size was the greatest contributor to missing cancers in obese men. Importantly, this bias may potentially be overcome by simply obtaining more cores at the time of biopsy in obese men or using a nomogram to determine the number of cores needed based upon prostate size.[19]

Ultimately, after adjusting for the lower PSA values and larger prostate sizes, obese men were nearly twice as likely to harbor prostate cancer as non-obese men. This is in-line with the 136% increased prostate cancer risk after multivariate adjustment seen in our prior study of veterans with a BMI >35 kg/m^2.[15] Regardless of the exact percentage, these data suggest that when factors related to prostate cancer detection are accounted for, obese men undergoing prostate biopsy are significantly more likely to have cancer than non-obese men. Moreover, obese men were 82% more likely to have high-grade cancer consistent with both prospective cohort and retrospective studies pointing towards obese men having higher grade tumors.[3–5,15,20–22] However, the p value in the current study suggests that our findings related to increased risk of high-grade cancer may be a chance finding. Of note, the current study had only 80% power to detect an OR for obesity of 2.5 or greater for high-grade disease. Thus, our study was underpowered to detect clinically meaningful differences and

thus these analyses related to risk of high-grade must be viewed as exploratory. Thus, the preponderance of the data would suggest that not only are obese men being underdiagnosed, but that they have more aggressive tumors at diagnosis. The degree to which delayed diagnosis due to detection bias versus biological causes explain the link between obesity and aggressive prostate cancer requires further study.

No follow-up data were available on our patients. Therefore, it is possible that some men with a negative biopsy actually harbored prostate cancer. Whether obesity influences the likelihood of finding cancer on repeat biopsy among these men is unknown. In the current study, we only examined data from men who were referred for and underwent a prostate needle biopsy and thus these results may not be generalizable to the whole population. Finally, the reduced detectability of prostate cancer among obese men is only relevant for asymptomatic clinically-localized disease. The association between obesity and metastatic disease, which usually presents symptomatically, would not be obscured by associations between BMI and prostate volume or PSA concentration.

CONCLUSIONS

Among a referral population of men undergoing a prostate needle biopsy in an equal access medical system, obese men had a lower PSA concentration and had a larger prostate volume. On crude analysis, obesity was not associated with prostate cancer risk. However, after adjusting for these clinical characteristics which may make detection of prostate cancer more difficult, obese men were nearly twice as likely to have prostate cancer. These findings suggest that detection bias issues may obscure the true positive association between obesity and prostate cancer development.

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TABLE 1

Clinical features of men undergoing prostate needle biopsy

	Non-obese	Obese	p value
Number of patients	318 (72%)	123 (28%)	
Age at biopsy ± SD(yr)	64.8 ± 8.4	63.4 ± 7.8	0.19
PSA (ng/ml)			0.02
Mean ± SD	8.0 ± 7.8	6.4 ± 5.2	
Median	6.0	5.0	
Prostate volume (cc)			0.04
Mean ± SD	41.5 ± 24.4	47.1 ± 29.3	
Median	35	40	
Number of biopsy cores obtained			0.22
Mean ± SD	10.7 ± 1.8	11.0 ± 1.9	
Median	12	12	
Race			0.37
White	161 (51)	67 (54)	
Black	116 (36)	46 (37)	
Other	41 (13)	10 (8)	
Abnormal rectal examination (n)			0.89
No	202 (64)	79 (64)	
Yes	116 (36)	44 (36)	

TABLE 2

Odds ratios (OR) and 95% confidence intervals of obesity for predicting prostate cancer detection on biopsy, or a high Gleason disease (≥4+3) among men with prostate cancer at the time of biopsy

	Obese vs. Non-obese			BMI as a continuous variable		
	Odds ratio*	**95% CI**	**p value**	**Odds Ratio**	**95% CI**	**p value**
Prostate Cancer Detection						
Crude analysis	1.13	0.73 – 1.75	0.58	0.99	0.95 – 1.03	0.74
Age-adjusted analysis	1.22	0.78 – 1.91	0.37	1.00	0.96 – 1.04	0.89
Multivariate-adjusted analysis**	1.98	1.17 – 3.32	0.01	1.06	1.01 – 1.11	0.02
Biopsy Gleason score ≥ 4+3						
Crude analysis	0.92	0.43 – 1.95	0.82	0.97	0.91 – 1.04	0.40
Age–adjusted analysis	1.05	0.49 – 2.27	0.90	0.99	0.92 – 1.06	0.72
Multivariate-adjusted analysis**	1.82	0.76 – 4.37	0.18	1.05	0.98 – 1.13	0.19

* Odds ratio for obese vs. non-obese

** Analysis adjusted for race, age, center, PSA, prostate volume, and DRE findings