Body Mass Index Affects the Diagnosis and Progression of Prostate Cancer in Hispanics

Rosa Negrón, MS; Andrea Vásquez, MS; Mariely Nieves, MS; Lourdes Guerrios, MD; Margarita Irizarry-Ramírez, PhD

Introduction: The occurrence of lower prostate-specific antigen (PSA) levels in overweight White and African American men has been studied, but there is no data regarding Hispanics, which have a higher mortality rate from Prostate Cancer (PCa) than Whites. The objective of this study was to investigate if being overweight could affect both the sensitivity of the PSA as a diagnostic tool and the progression of PCa in this group.

Methods: Retrospective study of records from 400 patients that underwent testing for PCa during 2005 and 400 patients under treatment for PCa from 2003–2005 at the urology clinics of the Veterans Administration Caribbean Healthcare System. Accrued data included body mass index (BMI), age, PSA levels, biopsy results, and cancer status after treatment.

Results: In men, with normal age adjusted PSA levels, overweight and obese men had 35.38% and 38.13%, respectively, positive biopsies while men with normal BMI had 26.15%. In addition, 73.84% of overweight men over 61 years old with normal PSA were positive for prostate cancer. There is a statistically significant decrease in PSA sensitivity from 71.7 (95% CI:58.6–82.5) in men with normal BMI to 55.4 (95% CI:41.5–68.7) in obese men (P=.015). In multivariate analysis, patients with a BMI over 25 kg/m^2 had a 2.63 (CI 95%: 1.23–5.64) fold higher risk of metastases than those with normal BMI.

Conclusions: In overweight Hispanic men the PSA level is a less sensitive marker for PCa and those individuals with higher BMI have higher prevalence of metastatic disease. (*Ethn Dis*. 2010;20[Suppl 1]:S1-168–S1-172)

Key Words: PSA, Prostate Cancer, Hispanics, BMI

From Graduate Department, Clinical Laboratory Sciences, School of Health Professions, Medical Sciences Campus, University of Puerto Rico (RN, AV); Clinical Research Center, Medical Sciences Campus, University of Puerto Rico (MN); Urology Section, School of Medicine, Medical Sciences Campus, University of Puerto Rico and Veterans Administration Caribbean Healthcare System (LG); and Graduate Department, Clinical Laboratory Sciences, School of Health Professions, Medical Sciences Campus, University of Puerto Rico (MIR).

Introduction

According to data from the National Cancer Institute, in the United States, the 2005 incidence rate of prostate cancer (PCa) per 100,000 was 116.4 for Hispanics and 132.8 for Whites and 210.5 for African Americans.[1] Death rates for Hispanics/Latinos in the United States reveal that this group has the third highest death rate from prostate cancer with 21.8 deaths per 100,000 males compared to African Americans with 68 and Whites with 26.22.[1] In Puerto Rico the incidence rate was 120.5 with a death rate per 100,000 males of 42.3.[2,3] Thus we have a conundrum; a lower incidence rate in males in Puerto Rico but a higher death rate when compared to Whites in the United States. We have been studying possible causes for this health disparity.

Obesity, particularly abdominal adiposity, may be related to progression of existing prostate cancer disease.[4] Obesity has been also associated with an increased risk of prostate cancer death.[5] In addition, recent studies found that obesity may be biologically associated with more aggressive prostate cancer and is also associated with increased prostate cancer development.[6,7] Overweight and obesity in the United States occur at higher rates in racial/ethnic minority populations such as African American and Hispanic Americans. In Puerto Rico, according to data from the Puerto Rico's Health Department published in May 2002, 58% (2,208,994) of the citizens are overweight and 20% are obese.[8]

The gold standard for prostate cancer diagnosis is the combination of prostate-specific antigen (PSA) level determination and a digital rectal examination (DRE). Factors that may impact PSA levels may have an impact in prostate cancer detection. In addition, cultural aspects may lower the number of men that have a DRE.

Baillargeon et al, in 2005, reported in a study that included White and African-American men, that lower PSA values may be masking PCa in overweight and obese men.[9] Werny et al compared PSA levels with anthropometric measures in White, Black and Mexican American men.[10] To our knowledge there is no information regarding PSA sensitivity, obesity and prostate cancer in a Hispanic population not of Mexican origin.

In the current study we tested the hypothesis that overweight and obese men in our population would present normal PSA values while still having PCa. In addition, we wanted to establish if an elevated body mass index (BMI) could also impact the progression of the disease after treatment and if it could affect the diagnosis of PCa.

Methods

This project was approved by the IRBs of the Veterans Administration Caribbean Heath System(VACHS) and UPR-Medical Sciences Campus (MSC).

We analyzed 800 records from the urology department of VACHS of patients that were diagnosed or treated between 2003–2005. Patient were aged

Address correspondence and reprint requests to Margarita Irizarry-Ramírez, PhD; Clinical Laboratory Sciences, School of Health Professions, Medical Sciences Campus; University of Puerto Rico; PO Box 365067; San Juan, Puerto Rico 00936-5067; 787-758-2525 Ext 7035; 787-758-6421 (fax); margarita.irizarry@upr.edu

46–89 years. Data extracted was BMI at diagnosis, BMI during and after treatment, PSA values at the time of diagnosis and after treatment, and metastasis status.

Body Mass Index

Body mass index was calculated according to Center for Disease Control formula (weight [kg]/height^2 [m^2]). Body mass index categories were normal (<22.9 kg/m^2), borderline (23.0–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (>30.0 kg/m^2), integrating the BMI definition by the World Health Organization and international variations proposed by US National Institutes of Health that adds a borderline category. For the purpose of our statistical analyses a BMI <25 kg/m^2 was considered normal BMI.

Population

We identified 400 patients that received treatment for prostate cancer at the VACHS from 2003–2005 and 400 patients that underwent testing for prostate cancer during 2005 at VACHS. Although the population was not selected to represent geographical areas, it was representative of the different areas in Puerto Rico since this health facility is the only major medical center for veterans on the island.

Prostate-Specific Antigen

The normal value for the PSA levels was defined using age specific ranges as follows: PSA<2.5ng/mL for men aged 41 to 50 years, PSA<3.5ng/mL for men 51–60, PSA<4.5ng/mL for men 61–70, PSA< 6.5ng/mL for men >70. These age-adjusted levels were used to establish all statistical relationships.

Statistical Analyses

Univariate analyses were performed using mean and standard deviations for continuous variables and frequencies and percentages for categorical variables. False-positive PSA frequency analysis was conducted among men who did not have prostate cancer (specificity analysis) as per their biopsy results and false-negative PSA among men who did (sensitivity analysis). Unconditional logistic regression was used to evaluate the magnitude of association between BMI groups and the outcome of PSA screening with BMI <25 kg/m^2 as a reference group and age as a confounder variable. The level of significance was $P<.05$. Relationships among the variables were tested with Wilcoxon Signed Ranked Test or Pearson chi-square, as appropriate. Multivariate logistic regression analysis was performed to evaluate the risk of metastases according to BMI category. Statistical significance was set at $P<.05$. SPSS® version 16.0 was used for statistical data analysis (SPSS Inc. Chicago Ill.).

Table 1. Loss of sensitivity of PSA in overweight/obese patients, *n*=400

	< 25 kg/m^2	25–29.9 kg/m^{2†}	> 30 kg/m^2
True negatives	53	96	57
False positives	28	59	25
True positives	59	71	56
False negatives	17	23	25
*Sensitivity (95%CI)	71.7(58.6–82.5)	67.6 (55.5–78.2) ‡	55.4 (41.5–68.7)§

* Unadjusted
† BMI 25–29 kg/m^2 vs BMI more than 30 kg/m^2 statistically significant $P=.004$
‡ BMI 25–29 kg/m^2 vs BMI more than 30 kg/m^2 statistically significant $P=.043$
§ BMI more than 30kg/m^2 vs BMI less than 25 kg/m^2 statistically significant $P=.015$
CI=Confidence interval

RESULTS

Of the 800 patients, 161 (20.2%) had a normal BMI, 57 (7.0%) had a borderline BMI, 372 (46.5%) were overweight and 210 (26.3%) were obese.

Of these 800 patients we included all (n=400) whose records included treatment protocol, metastasis information and living status. Of these 400 patients, in men with normal age-adjusted PSA levels, the percentage of positive biopsies was 35.38% in overweight men, 38.13% in obese men and 26.15% in men with normal BMI. In addition, 73.84% of overweight men aged >61 years with normal PSA presented positive with prostate cancer. Prostate-specific antigen sensitivity decreased in a statistically significant manner to 55.4 (95% CI, 41.5, 68.7) in obese men as compared to 71.7 (95% CI, 58.6, 82.5) in men with normal BMI ($P=.015$). (Table 1)

Table 2 summarizes the baseline characteristics of the studied population (n=400), stratified by age, BMI and PSA levels.

When we analyzed the data to assess if there was a difference, between the BMI groups, in the response to treatment as measured by a decrease in PSA levels, we found a significant decrease in the PSA levels of patients with a BMI <25kg/m^2 and a significant increase in the PSA levels among patients with a BMI ≥25kg/m^2 ($P<.001$). (Table 3)

Metastasis was found in 17% of overweight patients and in 20% of the obese patients but only in 10% of patients with normal BMI ($P=.05$). (Data not shown) Table 4 shows the univariate and multivariate analysis for the risk of developing metastasis by BMI category. In multivariate analysis, after adjustment for age and PSA levels at time of diagnosis; a 2.63 fold higher risk of metastases was observed among patients with a BMI≥25kg/m^2 as compared to patients with normal BMI (CI95%:1.23–5.64; $P<.05$). Higher PSA serum levels at time of diagnosis was found to have a .07% higher of risk of metastases and as age increased there was a 2.1 fold risk for

Table 2. Baseline characteristics of the study group

Variable	Total (*N*=400)	Metastases (*n*=63)	No Metastases (*n*=337)
Age			
Mean	69.78 (8.25)	69.23 (8.15)	72.73 (8.25)
Median	71.0	70.0	73.0
Range (max-min)	46.0–89.0	46.0–88.0	49.0–89.0
BMI, *n* (%)			
<25 kg/m^2	103 (25.8)	10 (15.9)	93 (27.6)
$\geq$ 25 kg/m^2	297 (74.2)	53 (84.1)	244 (72.4)
PSA levels			
Mean	23.83 (102.71)	73.21 (227.98)	14.59 (48.92)
Median	7.76	14.62	7.23
Range (max-min)	0.01–1715.0	0.10–1715.0	0.01–150.0

metastasis onset. Moreover, 18% of overweight/obese patients with normal PSA values adjusted by age at the time of diagnosis developed PCA metastases, compared to 4% of patients in the normal BMI category. (Data not shown) We also calculated the death risk in patients with bone metastasis. A 2.99 increased death risk was found in patients with bone metastasis.

DISCUSSION

Some previous studies have found no association between prostate cancer risk and BMI.[11–13] In contrast, other trials have demonstrated that men with an increased BMI have a greater risk of developing prostate cancer.[14–17] None of these studies looked at a Hispanic population.

Obesity is a major health problem in Puerto Rico[8] and prostate cancer mortality rates are higher than normal for our population. We hypothesized that overweight and obese men in our population would present lower PSA values while still having PCa and that this may be influencing the mortality rate.

Our cohort, when distributed by weight, followed the general population trend since 584 (73%) were overweight. Our results indicate that 76% of men over 61 years old and overweight had normal levels of PSA although they had PCa. We propose that in this overweight/obese population the reduced sensitivity of PSA as a diagnostic marker may be, by under diagnosis, augmenting the risk of PCa. Additionally, DRE accuracy has been shown to be affected by the patient's BMI since overweight men tend to have large prostate glands, making the detection of the cancer difficult in asymptomatic patients.[18] So the combination of lower PSA and inconclusive DRE may be responsible, in part, for the increasing risk of PCa in the overweight population.

Our data show that there is a relationship between obesity and metastasis development in the studied population. As mentioned before, the only group that demonstrated a statistically significant difference in the PSA values, before and after treatment, were individuals with normal BMI. The reduction of the PSA is the gold standard to monitor response to treatment. Failure in achieving this reduction is considered a biochemical recurrence. Thus in the overweight and obese group the risk of developing metastasis appears to be related to this biochemical recurrence. These data agree with what was found by Amling et al while studying groups of White and Black men.[19] Their data showed an association between obesity and adverse pathologic features and higher biochemical recurrence rates in men with PCa undergoing radical prostatectomy. They also suggested that obesity may play some role in determining the higher prevalence of advanced disease in Black men.

Other studies have tried to explain the relationship between high body fat percentage, including abdominal adiposity, and the risk for prostate cancer or death from the disease.[20] Obesity is known to affect levels of, among others, leptin, insulin and IGF-1 concentration in the serum, as well as inducing alterations on hormonal levels, including testosterone.[21–25]

The purpose of our study was to establish a relationship between overweight and the diagnosis and progression of prostate cancer. Our data suggest that in overweight and obese men the death risk is increased as well as the risk for misdiagnosis. We are aware that this study has limitations. One is a lack of information on the patient's history regarding his BMI. It would be impor-

Table 3. Response to treatment measured by change in PSA levels in BMI categories

BMI Category	PSA before treatment	PSA after treatment	Mean difference (before-after)	*P*-value
BMI$<$25kg/m^2, *n*=103				
Mean (SD)	23.13 (54.26)	13.69 (91.11)	9.44 (89.68)	$<$.001*†
Range (min-max)	.01–470.90	.00–904.00		
BMI$\geq$25kg/m^2, *n*=297				
Mean (SD)	24.07 (115.31)	27.11 (153.73)	−3.04 (143.73)	$<$.001*†
Range (min-max)	.10–1715.00	.00–1921.00		

* $P<.05$, Wilcoxon Signed Rank Test.

† A statistically significant decline in the PSA levels among patients with a BMI$<$25 kg/m^2 and a statistically significant increase in the PSA levels among patients with a BMI$\geq$25kg/m^2 was observed after treatment.

Table 4. Risk of metastasis by BMI Category

Variable	Univariable		Multivariable†	
	OR	CI (95%)	OR	CI (95%)
BMI				
<25 kg/m^2, *n*=103	1.00	-	1.00	-
≥25 kg/m^2, *n*=297	2.02	0.99–4.14	2.63	1.23–5.64*

* $P<.05$

† Model was adjusted by age and PSA level at time of diagnosis

N of metastases=63; 10 patients with normal BMI and 53 patients with BMI≥25kg/m^2.

tant to ascertain if changes in BMI throughout the lifetime may change the risk ratios found. Moreover BMI is not necessarily the best index since it misrepresents people with high lean body mass. In fact lean body mass may be a more accurate measure especially in studies related to diseases that may have a close relationship to androgens. In addition we did not evaluate other confounding variables such as smoking history and eating habits. Within the scope of this study we did not measure serum or plasma levels of the previously mentioned molecules, which could shed light into the biochemical status of these patients.

When we designed this study we chose patients from the VACHS, which provides free and easy access to medical care, thus differences within the subjects were not due to unequal access to medical services. The medical conditions of the general population are not comparable to this group. Current guidelines indicate that men should visit the urologist once a year after they are 40 years old, and obtain a PSA level and a rectal examination to rule out any malignancy in the prostate. Most men in our population depend on a health system that requires a referral from a general practitioner to visit a urologist. Thus, if these patients are asymptomatic, and obtain a normal PSA level, they could be misdiagnosed if their anthropometric measurements are not taken into account. In conclusion the increased death risk ratio in this overweight population may explain the higher death rate from prostate cancer in Puerto Rico. We propose that new diagnostic guidelines for prostate cancer should include the determination of body fat, or at least the BMI, before interpreting laboratory results or DRE results. In addition we need to develop aggressive public education campaigns to reduce obesity in the population as well as study the underlying molecular mechanisms that may explain the relationship between obesity and prostate cancer.

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