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OBESITY AND PROSTATE CANCER CLINICAL RISK FACTORS AT PRESENTATION: DATA FROM CaPSURE

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ABSTRACT

Purpose: We investigated the association of obesity with prostate cancer case demographics and clinical disease features at presentation.

Materials and Methods: Data were abstracted from CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor), a disease registry of 10,018 men with prostate cancer. A total of 2,952 men were included who were treated between 1989 and 2002, and had complete body mass index (BMI) information. BMI classes were defined as normal (less than 25 kg/m^2), overweight (25 to 29.9 kg/m^2), obese (30 to 34.9 kg/m^2) or very obese (35 kg/m^2 or greater). Patients were categorized as having low, intermediate or high risk disease based on the D'Amico classification. Associations among BMI, risk and demographics were analyzed using univariate and multivariate models.

Results: Of the patients 29% had a normal BMI, 51% were overweight, 16% were obese and 5% were very obese. Patients who were overweight or obese were more likely to be young, have hypertension and diabetes, and have a lower education level. The overweight group had a lower serum prostate specific antigen ($p = 0.010$) and lower stage disease ($p = 0.030$) at diagnosis, but there was no association between Gleason score and obesity ($p = 0.57$). However, among men with a BMI of 25 kg/m^2 or greater there was a positive correlation between increasing BMI and risk of being in a worse prognostic group at diagnosis ($p = 0.018$).

Conclusions: Overweight and obese patients are more likely to be young at diagnosis and have multiple comorbidities. Men in the overweight and obese groups presented with lower risk prostate cancer at diagnosis. This may be due to earlier disease detection secondary to more frequent interaction with the medical community. Among overweight and obese patients increased obesity is associated with a slightly increased chance of having high risk prostate cancer at diagnosis.

KEY WORDS: prostatic neoplasms, body mass index, obesity, risk

Obesity is a growing public health concern affecting more than 30% of men in the United States.[1] The relationship of obesity to prostate cancer risk is controversial with some studies indicating that obesity is associated with a decreased incidence of prostate cancer[2] while others suggest increased incidence[3] and worse prostate cancer survival in obese men.[4] The effect of obesity on pathological variables and outcomes after radical prostatectomy has been recently examined. Three multicenter studies suggest obesity is related to adverse pathological features at radical prostatectomy[5,6] and an increase in prostate specific antigen (PSA) recurrence after radical prostatectomy.[7] Potential flaws in those studies relate to selection bias since many obese or higher risk patients may not be treated surgically.

The possible mechanisms of increased prostate cancer risk with obesity include a direct effect of dietary or physical activity factors or an effect on the hormonal axis. Obesity has been associated with lower testosterone levels[8] which have been associated with higher pathological stage in men with prostate cancer.[9] Obesity is also associated with higher levels of serum leptin,[10] insulin and insulin-like growth factor 1,[11] all of which may be mitogenic.

Because the relationships of obesity to important demo-

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graphic factors such as race[5] and socioeconomic status[12] are complex, and may affect prostate cancer risk, treatment and progression, it is important to analyze these factors. We evaluated the relationships of obesity to demographic and prostate cancer disease risk variables using a large longitudinal observational prostate cancer database.

MATERIALS AND METHODS

CaPSURE is a longitudinal, observational database of men with biopsy proven prostate adenocarcinoma recruited from 35 academic and community based urology practices across the United States. All patients with prostate cancer are recruited consecutively by participating urologists who report complete clinical data and followup information on diagnostic tests and treatments. Data for patients diagnosed before 1995 but still followed by a urologist were initially entered retrospectively and for those diagnosed since 1995 all data entry has been prospective. Informed consent is obtained from each patient under local institutional review board supervision. Patients are treated according to their physicians' usual practices and are followed until death or withdrawal from study. Completeness and accuracy of the data are assured by random sample chart review every 6 months. Additional project methodology details have been reported previously.[13]

For the comparison of high risk prostate cancer disease presentation and body mass index (BMI), 2,952 men were included in the analysis. They were treated between 1989 and 2002, and had complete BMI information. BMI classes were defined as normal (less than 25 kg/m^2), overweight (25 to 29.9 kg/m^2), obese (30 to 34.9 kg/m^2) or very obese (35 kg/m^2 or greater). Patients were categorized as having low, intermediate or high risk disease based on a modification of the D'Amico classification.[14] Cases were categorized as low (T1–T2a, PSA less than 10 ng/ml and Gleason grade less than 7 [no Gleason pattern 4 to 5 disease]), intermediate (T2b, T2c, PSA 10 to 20 ng/ml or Gleason grade 7) or high risk (T3–4, PSA greater than 20 ng/ml or Gleason grade 8 to 10). Associations among obesity, risk and demographics were analyzed using univariate and multivariate models. For categorized variables (ethnicity, race, relationship status, smoking status, alcohol status and comorbidity status) the chi-square test was used. For ordinal and categorized continuous variables (BMI, age, education level, household income status, Gleason grade, PSA at diagnosis, T stage and prognostic risk categorization) the Mantel-Haenszel chi-square test was used. Odds ratios were calculated using multivariate logistic regression analysis. All analyses were conducted using SAS version 8.2 (SAS Institute, Cary, North Carolina).

RESULTS

Mean BMI was 27.2 kg/m^2 with a standard deviation of 4.2 and a range of 13 to 48 kg/m^2. A total of 1,014 (29%) patients had a normal BMI, 1,752 (50%) were overweight, 552 (16%) were obese and 168 (5%) were very obese. Of the patients 89% were white, 8% were black and 3% were other. Average age of the cohort was 66.5 years. Average age ± SD of the cohort was 66.2 ± 8.8 years (range 40 to 92). In table 1 we present descriptive data on baseline demographic features of the study population and univariate associations with BMI. Table 2 lists the clinical characteristics of the study population and associations with BMI. A significant association was found between BMI and age ($p < 0.0001$), education status ($p = 0.02$), smoking ($p = 0.001$), alcohol status ($p = 0.02$), hypertension ($p < 0.0001$) and diabetes ($p < 0.0001$). Patients who were obese were more likely to be young, have hypertension and diabetes, and have a lower education level. No significant association was found between BMI and household income, relationship status and heart disease. Race was also not found to be associated with BMI ($p = 0.43$).

In table 3 we investigated the association between BMI and the likelihood of presenting in a high risk prognostic group at diagnosis, controlling for clinical and demographic factors. We used logistic regression to predict prognostic category (high risk versus low and moderate risk), adjusting for age, ethnicity, education, income, relationship status, smoking, alcohol and comorbidities. After adjusting for age, ethnicity, education, income, relationship status, smoking, alcohol and comorbidities, men in the overweight group (25 to 29.9 kg/m^2) were less likely to be in the high risk prognostic category compared to men of normal weight, but the effect fell short of statistical significance (odds ratio 0.82, $p = 0.065$). After adjusting for demographic and clinical variables the overweight group also had a lower PSA ($p = 0.010$) and lower stage disease ($p = 0.030$) at diagnosis, but there was no association between Gleason score and obesity ($p = 0.57$). The obese and very obese groups had a similar chance of being in the high risk prognostic category compared to the normal group. Table 3 lists the test outcomes (odds ratios and p values) for comparisons of the chance of overweight, obese and very obese categories of BMI to present in the high risk prognostic category compared to normal weight men. In this multivariate model older age, positive smoking history, black race and low household income also conferred a greater risk of presenting with higher risk prostate

TABLE 1. *Demographic characteristics and association with BMI*

Variable	No. Normal (%)	No. Overweight (%)	No. Obese (%)	No. Very Obese (%)	p Value (chi-square test)
Race:					0.43
White	778 (28.6)	1,384 (50.9)	426 (15.7)	130 (4.8)	
Black	65 (27.8)	112 (47.9)	41 (17.5)	16 (6.8)	
Age:					<0.0001
Younger than 60	164 (23.1)	360 (50.6)	134 (18.9)	53 (7.5)	
60–64	132 (25.3)	265 (50.9)	85 (16.3)	39 (7.5)	
65–69	173 (26.8)	323 (50.0)	124 (19.2)	26 (4.0)	
70–74	147 (28.0)	294 (55.9)	67 (12.7)	18 (3.4)	
75 or Older	227 (41.4)	254 (46.4)	57 (10.4)	10 (1.8)	
Marital status:					0.32
Married/significant other	740 (28.0)	1,351 (51.1)	419 (15.9)	132 (5.0)	
Single/divorced/widowed	103 (33.2)	145 (46.8)	48 (15.5)	14 (4.5)	
Education completed:					0.02
High school or less	364 (28.6)	624 (48.9)	223 (17.5)	64 (5.02)	
Some college	159 (26.9)	291 (49.2)	108 (18.3)	33 (5.6)	
College graduate	144 (29.9)	247 (51.2)	70 (14.5)	21 (4.4)	
Graduate/professional school	176 (29.1)	334 (55.3)	66 (10.9)	28 (4.6)	
Household income:					0.18
$0–$20,000	161 (31.9)	244 (48.3)	82 (16.2)	18 (3.6)	
$20,000–$50,000	366 (28.8)	635 (50.0)	209 (16.4)	61 (4.8)	
Greater than $50,000	316 (26.87)	617 (52.5)	176 (15.0)	67 (5.7)	

TABLE 2. *Clinical and pathological characteristics and associations with BMI*

Variable	No. Normal (%)	No. Overweight (%)	No. Obese (%)	No. Very Obese (%)	p Value (chi-square test)
Smoking status:					0.001
Yes	124 (39.2)	138 (43.7)	37 (11.7)	17 (5.4)	
No	716 (27.3)	1,351 (51.5)	429 (16.4)	128 (4.9)	
Alcohol consumption:					0.02
Yes	499 (28.4)	920 (52.4)	265 (15.1)	71 (4.1)	
No	335 (28.5)	568 (48.3)	199 (16.9)	75 (6.4)	
Heart disease:					0.89
No	678 (28.7)	1,202 (50.9)	368 (15.6)	116 (4.9)	
Yes	165 (28.1)	294 (50.0)	99 (16.8)	30 (5.1)	
Diabetes:					<0.0001
No	788 (29.9)	1,348 (51.1)	395 (15.0)	108 (4.1)	
Yes	55 (17.6)	148 (47.3)	72 (23.0)	38 (12.1)	
Hypertension:					<0.0001
No	579 (34.8)	846 (50.8)	193 (11.6)	48 (2.9)	
Yes	264 (20.5)	650 (50.5)	274 (21.3)	98 (7.6)	
PSA at diagnosis (ng/ml):					0.010
0–4	95 (23.0)	224 (54.2)	63 (15.3)	31 (7.5)	
4.1–10	463 (28.2)	862 (52.4)	244 (14.8)	75 (4.6)	
10.1–20	130 (31.0)	190 (45.4)	79 (18.9)	20 (4.8)	
Greater than 20	101 (37.8)	115 (43.1)	44 (16.5)	7 (2.6)	
Pathological Gleason sum:*					0.57
2–6	516 (27.6)	984 (52.7)	286 (15.3)	81 (4.3)	
7	201 (27.9)	354 (49.2)	117 (16.3)	48 (6.7)	
8–10	92 (35.0)	111 (42.2)	49 (18.6)	11 (4.2)	
Pathological tumor stage:*					0.030
T1	292 (25.4)	602 (52.4)	199 (17.3)	55 (4.8)	
T2	425 (29.4)	731 (50.5)	220 (15.2)	72 (5.0)	
T3	50 (41.0)	53 (43.4)	15 (12.3)	4 (3.3)	
T4	5 (62.5)	0 (0.0)	2 (25.0)	1 (12.5)	

* According to the 2002 American Joint Committee on Cancer Cancer Staging Manual.

TABLE 3. *Likelihood of presenting with high risk disease in multivariate analysis*

	Odds Ratio	p Value (logistic regression)
BMI category:		
Normal	1.00	
Overweight	0.82	0.065
Obese	1.02	0.90
Very obese	1.10	0.68
Black race	1.98	0.0001
Age at diagnosis:		
75 or Older	1.00	
70–74	0.63	0.0005
65–69	0.40	<0.0001
60–64	0.37	<0.0001
Younger than 60	0.28	<0.0001
Household income:		
Greater than $50,000	1.00	
$20,000–$50,000	1.20	0.13
$0–$20,000	1.82	0.0001
Education completed:		
Some college	1.00	
High school or less	0.95	0.67
College graduate	1.18	0.29
Graduate/professional school	0.77	0.09
Single/divorced/widowed	1.19	0.22
Pos smoking history	1.42	0.016
Alcohol consumption	1.13	0.21
Hypertension	1.05	0.64
Heart disease	0.92	0.46
Diabetes	0.99	0.97

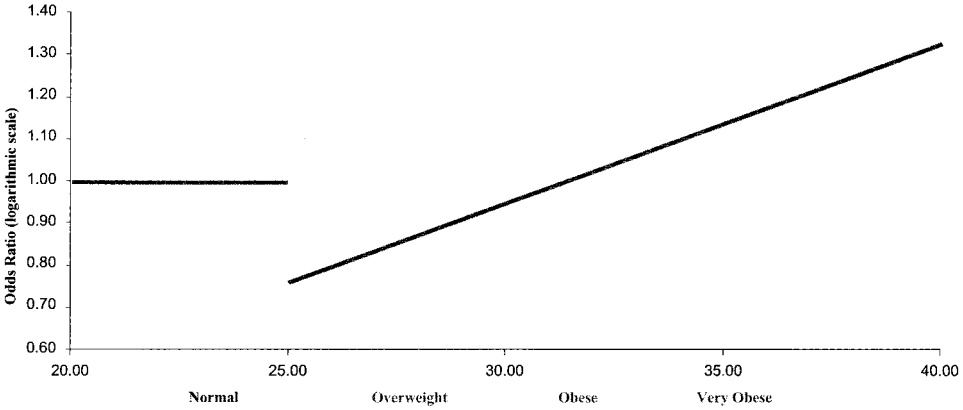
cancer. Education level, relationship status, alcohol status and comorbidity status (known diabetes, hypertension or heart disease) were not associated with higher risk prostate cancer at diagnosis.

We then analyzed how the odds of being in the high risk group at diagnosis varied with continuous BMI separately within each BMI category. After adjusting for demographic and clinical variables we found that the slope within the normal group was not significantly different from 0 ($p = 0.22$). Therefore, the chance of falling in the high risk group did not change significantly with BMI for patients with BMI less than 25 kg/m^2. Furthermore, we found that slopes and intercepts were not significantly different between the overweight and obese groups. This allowed us to construct an overall trend line for BMI greater than 25 kg/m^2 and the odds of being in the high risk prognostic category. The resulting simplified model is shown in the figure. We found that overweight, obese and very obese patients had an increased chance of being high risk at diagnosis with increasing BMI ($p = 0.018$) using logistic regression with the same covariates.

DISCUSSION

The prevalence of obesity is increasing in the United States and constitutes a major public health concern.[1] Obesity is associated with increased hypertension, diabetes, heart disease,[15] arthritis and an increased risk of a number of malignancies including those of breast and colon.[16] The relationship between obesity and prostate cancer is less clear and a number of contradictory studies have been published.

Our study illustrates the significant demographic differences of overweight and obese patients with prostate cancer compared to those of normal weight. Overweight and obese patients were more likely to be young, less educated, and have hypertension and diabetes. When analyzing individual prostate cancer risk parameters we observed a surprising result. Overweight and obese patients were diagnosed with lower serum PSA and lower clinical stage but disease grade was similar to that of normal weight patients. This may represent a bias of earlier detection among overweight and obese patients. Perhaps obese patients have more interaction with the medical community due to comorbidities, or possibly there is more suspicion of disease in obese patients on the part of physicians. We did not have information on age at first PSA or other screening behavior to address this issue. The other possibility explaining diagnosis at an earlier age is increased prostate cancer initiation or progression related to obesity. However, lower clinical stage and PSA at diagnosis do not support this theory.



Odds of classification in high risk prognostic category for continuous BMI less than 25 and greater than 25 ($p = 0.018$)

In multivariate analysis overweight men were not more likely to present with high risk prostate cancer than men with a normal BMI (RR 0.82, $p = 0.065$). However, among overweight and obese men increasing obesity appeared to increase the risk of being diagnosed with high risk features ($p = 0.018$). These data suggest earlier diagnosis in overweight patients with resulting lower risk at presentation, while at the same time imply that increasing obesity may actually increase prostate cancer disease risk.

Four of the largest previous studies on the relationship between obesity and prostate cancer risk reported conflicting results. In a retrospective cohort study of 2,368 Swedish construction workers followed for 18 years, BMI was more strongly associated with prostate cancer mortality than incidence.[4] When comparing highest and lowest BMI categories the relative risk was 1.40 (CI 1.09–1.81). This cohort was particularly young with more than 50% of the participants younger than 40 years upon admission to the trial.[17] Three other studies compared BMI to the risk of developing prostate cancer. Giovannucci et al (Health Professionals Follow-up Study) compared various anthropometric measurements at different stages of life to prostate cancer risk among 1,369 men.[18] This study demonstrated that BMI and waist-to-hip ratios were not related to the risk of prostate cancer. However, they did find that preadult obesity was associated with a lower risk of advanced and metastatic prostate cancer (RR 0.16, CI 0.05–0.54). In the Netherlands Cohort Study in which 631 men with prostate cancer were followed for a mean of 6.3 years, BMI and lean body mass at age 20 were not associated with increased prostate cancer risk.[3]

Two recent studies examined the association of obesity and pathological parameters at radical prostatectomy and biochemical outcomes. Using the Center for Prostate Disease Research database,[6] Amling et al found that obesity and race predicted adverse pathology. However, on multivariate analysis only race persisted as an independent predictor of adverse pathology. In an analysis of the Shared Equal Access Regional Cancer Hospital database, a multicenter surgical database of men treated primarily in the Veterans Affairs Health Care System, Freedland et al found that obesity was an independent predictor of biochemical recurrence after radical prostatectomy and the increased risk appeared at a threshold greater than BMI 27.5 kg/m^2.[7] This may partially be an effect of the difficulty of surgery in the very obese.

Our study is unique in a number of ways. It includes all patients entered into the database regardless of treatment and, therefore, includes a broader range of ages, comorbidities and prostate cancer risk parameters at diagnosis than a single treatment modality study. Also, the demographic and socioeconomic information in the database is extremely detailed, and allows internal validation of the established associations among BMI and other chronic diseases such as hypertension and diabetes. To our knowledge it is the first study that suggests that obese patients may be diagnosed at a younger age, and at a lower PSA and stage than nonobese patients. We hypothesized that this may be due to increased interactions with the medical community and a screening bias, although specific screening behavior was not measurable within the database. Finally, our analysis adds to the growing evidence of an increase in high risk prostate cancer with increasing levels of obesity.

The major caveat which must be borne in mind in interpreting these results, is that while CaPSURE does represent a mix of locales and practice types, the sites have not been chosen at random and, thus, the patients cannot be assumed to represent a statistically valid sample of the national population. For example, while patients are relatively overrepresented in CaPSURE compared with national census data. Furthermore, only men seen by urologists at the various sites are accessioned to CaPSURE. Thus, patients seen only by medical oncologists or other practitioners would not be included in study. Despite these cautionary notes we believe our data represent one of the best available samplings of patients with prostate cancer across the nation.

CONCLUSIONS

Overweight and obese patients are more likely to be young and have multiple comorbidities at prostate cancer diagnosis. Men in the overweight and obese groups presented with lower serum PSA and clinical stage prostate cancer. Among overweight and obese patients increasing obesity is associated with a slightly increased chance of having high risk prostate cancer at diagnosis.

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