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IMPACT OF OBESITY ON PROSTATE CANCER RECURRENCE AFTER RADICAL PROSTATECTOMY: DATA FROM CaPSURE

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ABSTRACT

Objectives. To determine the association between obesity and prostate cancer recurrence after primary treatment with radical prostatectomy.

Methods. Data were abstracted from CaPSURE, a disease registry of 10,018 men with prostate cancer. We included 2131 men who had undergone radical prostatectomy between 1989 and 2003 and had body mass index (BMI) information available. Recurrence was defined as two consecutive prostate-specific antigen (PSA) levels of 0.2 ng/mL or greater or any second treatment. Patients were risk stratified using the PSA level, Gleason grade, and clinical T stage.

Results. Patients were followed up for a median of 23 months. Of the 2131 patients, 251 (12%) developed recurrence at a median of 13 months (range 1 to 107); 183 (9%) of these men had PSA failure and 68 (3%) received a second treatment. After adjusting for risk group, ethnicity, age, and comorbidities, a significant association was found between an increasing BMI and disease recurrence ($P = 0.028$). Very obese patients (BMI 35 kg/m^2 or more) were 1.69 times more likely to have recurrence relative to men of normal weight (BMI less than 25.0 kg/m^2; 95% confidence interval [CI] 1.01 to 2.84). An increasing PSA level ($P < 0.0001$) and Gleason grade ($P < 0.0001$) were also associated with recurrence. Ethnicity was not significantly associated with either BMI or PSA recurrence ($P = 0.685$ and $P = 0.068$, respectively).

Conclusions. The results of our study have shown that obesity is an independent predictor of prostate cancer recurrence. Because of the increased comorbidities and greater rates of recurrence, obese individuals undergoing radical prostatectomy need vigilant follow-up care. UROLOGY **66:** 1060–1065, 2005. © 2005 Elsevier Inc.

The prevalence of obesity has increased dramatically in the United States during the past two decades, from 13% in 1980 to 30% in 2000.[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] and other studies suggesting an increased incidence of prostate cancer[3–5] and worse prostate cancer survival among obese men.[3–5] Two recent, retrospective, multi-institutional studies have reported greater recurrence rates among obese patients after radical prostatectomy (RP).[6,7] Obesity was an independent predictor of recurrence in one but not in the other. We sought to evaluate the independent relationship of obesity to prostate cancer recurrence after treatment with RP using a large, community-based prostate cancer database.

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MATERIAL AND METHODS

The Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) is a longitudinal, observational database of men with biopsy-proven prostate adenocarcinoma, recruited from 31 academic and community-based urology practices across the United States. At each site, all patients with prostate cancer are enrolled consecutively by participating urologists, who report complete clinical data at accession and follow-up

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TABLE I. *Demographic and clinical characteristics*

Variable	Normal Weight (<25 kg/m^2)	Overweight (25–29.9 kg/m^2)	Obese (30–34.9 kg/m^2)	Very Obese (≥35 kg/m^2)	*P* Value
Patients (n)	548 (25.5)	1126 (52.3)	365 (17.0)	113 (5.3)	
Ethnicity					0.65
White	505 (25.9)	1015 (52.1)	328 (16.8)	101 (5.2)	
African American	29 (20.7)	74 (52.9)	27 (19.3)	10 (7.1)	
Other	14 (22.2)	37 (58.7)	10 (15.9)	2 (3.2)	
Age* (yr)	62.1 ± 7.2	61.4 ± 7.0	61.4 ± 6.3	58.6 ± 6.0	<0.0001
Clinical T stage					0.46
T1	242 (23.9)	533 (52.7)	189 (18.7)	47 (4.7)	
T2	270 (27.1)	514 (51.7)	153 (15.4)	58 (5.8)	
T3	11 (29.7)	20 (54.1)	4 (10.8)	2 (5.4)	
T4	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	
PSA level (ng/mL)					0.14
<4	101 (23.3)	221 (50.1)	81 (18.7)	31 (7.1)	
4–10	360 (25.8)	748 (53.6)	221 (15.8)	66 (4.7)	
10–20	65 (26.1)	121 (48.6)	49 (19.7)	14 (5.6)	
>20	22 (29.7)	36 (48.7)	14 (18.9)	2 (2.7)	
Biopsy Gleason score					0.42
≤6	378 (25.0)	810 (53.6)	249 (16.5)	75 (5.0)	
7	129 (25.9)	248 (49.8)	88 (17.7)	33 (6.6)	
8–10	31 (31.0)	45 (45.0)	19 (19.0)	5 (5.0)	
Comorbidities					
Hypertension	140 (16.5)	441 (52.1)	196 (23.1)	70 (8.3)	<0.0001
Diabetes	29 (16.9)	80 (46.5)	43 (25.0)	20 (11.6)	<0.0001
Heart disease	77 (26.6)	149 (51.7)	47 (16.3)	16 (5.5)	0.95
Comorbidity count					<0.0001
≤1	335 (28.3)	640 (54.2)	160 (13.5)	47 (4.0)	
2–3	177 (21.9)	410 (50.8)	167 (20.7)	53 (6.6)	
>3	36 (22.1)	76 (46.6)	38 (23.3)	13 (8.0)	

KEY: PSA = prostate-specific antigen.
Data presented as number of patients, with percentages in parentheses, unless otherwise noted.
** Mean ± SD.*

visits. The data for patients diagnosed before 1995 were initially entered retrospectively; for those diagnosed since 1995, all data entry has been prospective. Each patient provides informed consent under local institutional review board supervision. Patients are treated according to their physicians' usual practices and are followed up until death or withdrawal from the study. The completeness and accuracy of the data are ensured by random sample chart review every 6 months. Additional details about the registry have been previously reported.[8,9]

We included 2131 men who received RP between 1989 and 2002 as a primary treatment, without neoadjuvant or adjuvant therapy, and who had complete BMI information in the analysis. The 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), and very obese (35 kg/m^2 or more). Patients were categorized as having low, intermediate, or high-risk disease using the stratification system described by D'Amico *et al.*[10] Recurrence was defined as two consecutive serum PSA levels of 0.2 ng/mL or more or documentation of any second treatment at least 6 months after RP (patients receiving a second treatment sooner than 6 months after RP were determined to have received adjuvant therapy and were therefore excluded). The date of recurrence was defined as the date of the first PSA level that was 0.2 ng/mL or greater or the date of second treatment; patients without recurrence were censored at the date of the last recorded PSA level.

Disease-free survival was estimated using the Kaplan-Meier method and compared among the four BMI groups. The association between obesity and prostate cancer recurrence was analyzed using univariate and multivariate models. For categorical variables (ethnicity, comorbidity status), the chi-square test was used. For ordinal and categorized continuous variables (BMI, age, Gleason grade, PSA at diagnosis, T stage, and prognostic risk categorization), the Mantel-Haenszel chi-square test was used. For multivariate analysis, a forward, stepwise Cox proportional hazards model was used; the model controlled for risk group, PSA, Gleason grade, ethnicity, age, and comorbidities. PSA recurrence-free survival curves were estimated using the Kaplan-Meier method. All analyses were conducted using Statistical Analysis Systems, version 8.2, software (SAS Institute, Cary, NC).

RESULTS

For the 2131 patients who received RP as primary treatment, the median follow-up time was 23 months (mean 29, range 1 to 107). The mean BMI was 27 ± 4 kg/m^2 (range 13 to 47). Of the 2131 patients, 17% were obese and 5% were very obese. The average age at diagnosis was 61 ± 7 years (range 40 to 80). Recurrence developed in 251 (12%) patients; 183 (9%) had recurrence according to the PSA criteria and 68 (3%) received second treatment. The median time to recurrence was 13 months (range 0.5 to 83). Table I lists the baseline

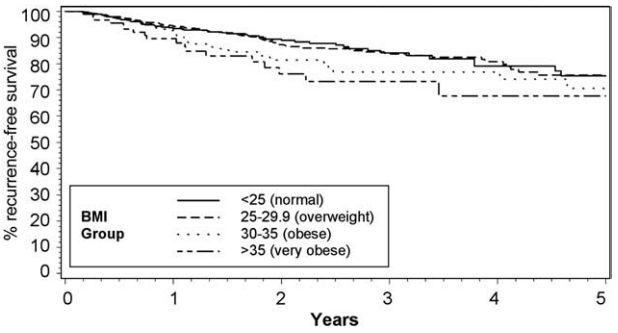

FIGURE 1. *Five-year biochemical recurrence estimates by BMI group. Actuarial survival determined by Kaplan-Meier analysis.*

demographic and clinical features of the study population.

Figure 1 presents the survival curves for patients in each BMI group. Log-rank survivorship analysis demonstrated that the BMI group correlated significantly with the risk of prostate cancer recurrence, with very obese patients having the greatest risk of recurrence ($P = 0.026$). Two-way log-rank comparisons revealed that those in the overweight group had outcomes similar to those of men with normal weight ($P = 0.754$). Patients in the obese group had slightly greater recurrence rates compared with patients in the normal-weight group, although this did not reach statistical significance ($P = 0.090$). A somewhat stronger trend was noted for patients in the very obese group to have greater recurrence rates than patients in the normal-weight group ($P = 0.056$).

On multivariate analysis, ethnicity was not associated with BMI ($P = 0.68$). The analysis of BMI as a continuous variable demonstrated a significant association between an increasing BMI and disease recurrence ($P = 0.028$). Patients with a BMI greater than 30 kg/m^2 had a 1.31-fold increased risk of recurrence compared with patients with a BMI less than 30 kg/m^2 (95% CI 1.004 to 1.708). Very obese patients were 1.69 times more likely than men in the normal-weight group to develop recurrence (95% CI 1.010 to 2.841). When analyzing the clinical data in multivariate analysis of the surgical cohort, an elevated PSA level ($P < 0.001$) and Gleason grade ($P < 0.001$) were also significant independent predictors of recurrence. A nonsignificant association was found between African-American ethnicity and recurrence (hazard ratio 2.33, 95% CI 0.939 to 5.795, $P = 0.068$); age, stage, hypertension, diabetes, heart disease, and comorbidity count did not predict for treatment failure. Table II presents the relationship between the clinical factors and prostate cancer recurrence.

COMMENT

Data from the most recent National Health and Nutrition Examination Survey (NHANES III) have demonstrated that 31% of American adults aged 20 years and older are obese (BMI greater than 30) up from 13% in 1980.[1] This epidemic of obesity is a problem relevant to urologists. In one study, the rise in the prevalence of obesity among patients undergoing RP as primary treatment of prostate cancer paralleled the overall national increase in obesity: nearly 26% of patients treated between 2000 and 2002 had a BMI of 30 kg/m^2 or more compared with 13% among those treated between 1988 and 1990.[7]

Despite the controversial relationship between obesity and prostate cancer incidence, several studies have suggested that men with a greater body mass have worse outcomes. In a study of 135,000 Swedish construction workers[3] and in two large American Cancer Society cohorts,[11] the prostate cancer mortality rates were consistently greater in patients with a greater BMI, suggesting a greater influence of body mass on prostate cancer aggression, rather than on prostate cancer incidence.[6] Likewise, an analysis from CaPSURE previously found a positive correlation between a greater BMI (>25 kg/m^2) and the risk of being in a worse prognostic group at diagnosis ($P = 0.018$).[12]

It is less clear how obesity affects prostate cancer outcomes after RP. In the current study, an increasing BMI was associated with an increased risk of prostate cancer recurrence. Very obese patients had a 1.69-fold greater risk of recurrence than men of normal body size. The trend toward an increased risk of recurrence among African-American patients suggests that ethnicity may independently predict outcome; however, the strength of this association remains unclear. We did not control for income and education, which are strongly associated with ethnicity, and which may contribute to worse outcomes among African Americans.

Recently, two other large, multi-institutional studies have explored the relationship between obesity and prostate cancer recurrence (Table III). Amling *et al.*[6] analyzed 3162 patients from the Center for Prostate Cancer Research database who underwent RP between 1987 and 2002. Two BMI categories were used for the analysis: the normal and overweight patients were combined to form one group (BMI less than 30 kg/m^2) and compared with the obese group (BMI greater than 30 kg/m^2). On univariate analysis, BMI was associated with a greater risk of biochemical recurrence. They also found that African Americans had an increased chance of being obese, as well as a greater risk of recurrence. In a multivariate analysis of ethnicity, BMI, and pathologic factors, African-American

TABLE II. *Factors predicting time to recurrence after radical prostatectomy*

Variable	Hazard Ratio	95% CI	*P* Value
Clinical stage			
T1–T2a	1.000		
T2b–T2c	1.042	0.789–1.375	0.773
T3–T4	1.322	0.625–2.802	0.466
PSA (ng/mL)			
<4	1.000		
4–10	1.134	0.756–1.701	0.543
10–20	3.104	1.985–4.852	0.0001
>20	3.720	2.147–6.445	0.0001
Biopsy Gleason score			
≤6	1.000		
7	1.764	1.304–2.387	0.0002
8–10	3.707	2.417–5.686	0.0001
Age	0.997	0.997–1.017	0.767
Ethnicity (AA)	2.333	0.939–5.795	0.068
Comorbidities			
Hypertension	1.041	0.764–1.418	0.799
Diabetes	1.177	0.727–1.905	0.508
Heart disease	1.271	0.836–1.931	0.261
BMI (continuous)	1.197	1.020–1.405	0.028
BMI (categorical) (kg/m^2)			
<25	1.000		
25–29.9	0.997	0.742–1.338	0.982
30–34.9	1.363	0.934–1.988	0.107
≥35	1.694	1.010–2.841	0.046
<30	1.000		
>30	1.310	1.004–1.708	0.047

KEY: CI = confidence interval; PSA = prostate-specific antigen; AA = African American; BMI = body mass index.

TABLE III. *Comparison of independent predictors of recurrence after radical prostatectomy; results from available studies analyzing body mass index*

Reference	Hazard Ratio	95% CI	*P* Value
Freedland *et al.*[7]			
PSA	1.79	1.47–2.18	<0.001
Biopsy Gleason score	1.34	1.20–1.50	<0.001
BMI	1.03	1.00–1.06	0.05
BMI ≥35 relative to <25	2.09	1.30–3.37	0.002
Amling *et al.*[6]			
Pathologic T stage	1.80	1.49–2.18	<0.001
Pathologic Gleason score	1.29	1.18–1.41	<0.001
African-American ethnicity	1.22	1.03–1.45	0.021
Current study			
PSA 10–20 ng/mL	3.10	1.98–4.85	<0.001
PSA >20 ng/mL	3.72	2.15–6.45	<0.001
Biopsy Gleason score 7	1.76	1.30–2.39	<0.001
Biopsy Gleason score 8–10	3.71	2.41–5.69	<0.001
BMI	1.20	1.02–1.41	0.028
BMI ≥35 relative to <25 kg/m^2	1.69	1.01–2.84	0.046
BMI ≥30 relative to <30 kg/m^2	1.31	1.00–1.70	0.047

KEY: PSA = prostate-specific antigen; BMI = body mass index.

ethnicity remained a significant independent predictor of recurrence. The investigators suggested that obesity in the African-American population may, in part, underlie the increased prostate cancer risk among African Americans.[6] In our study, the association between ethnicity and either BMI or

PSA recurrence was not statistically significant. This was likely due to the relatively low number of African Americans in our database.

Freedland *et al.*,[7] using the Shared Equal Access Regional Center Hospital Database Study Group, explored patient outcomes in 1106 men undergoing RP between 1988 and 2002. Obesity was again related to ethnicity, with African Americans having the greatest likelihood of being obese. Their study also found that a BMI of 35 kg/m^2 or greater conferred a greater risk of positive surgical margins. On multivariate analysis, controlling for ethnicity, positive margins, year of surgery, and preoperative clinical factors, a BMI of 35 kg/m^2 or greater remained a significant independent predictor of PSA failure. After patients were divided into groups by each 2.5-kg/m^2 separation in BMI, the risk of PSA failure did not dramatically increase until the BMI was 35 kg/m^2 or greater. Patients in the tier below the 35 kg/m^2 or greater group had a 15% chance of recurrence at 3 years, and those in the 35 kg/m^2 or greater group had a nearly 60% chance of recurrence at 3 years.[7] In our data set, very obese patients (BMI 35 kg/m^2 or greater) were 1.69 times more likely to have recurrence relative to men of normal weight (BMI less than 25.0 kg/m^2).

Multiple mechanisms may account for the increased prostate cancer recurrence among obese patients. One hypothesis invokes the direct effect of excess adipose tissue on the hormonal axis, leading to more aggressive tumor biology. Adipocyte aromatase converts testosterone to estrogen, reducing the testosterone/estrogen ratio. Obesity has been associated with lower testosterone levels,[13] which in turn have been associated with a worse pathologic stage in men with prostate cancer.[14] Obesity is also associated with greater serum levels of leptin,[15] insulin, and insulin-like growth factor 1 levels,[16] all of which may be mitogenic. Recurrence is clearly affected by ethnicity, but the magnitude of the independent contribution to recurrence risk conferred by ethnicity remains to be determined. Others have suggested that increased recurrence in the obese may be a result of a delayed diagnosis.[17] Obese patients tended to be younger and have more comorbidities. However, we found no association between the risk of prostate cancer recurrence and common conditions closely related to obesity, such as diabetes,[18] hypertension,[19] and heart disease.[20] Finally, prostate cancer recurrence may be related to the technical difficulties in performing optimal prostate resection and lymph node dissection in an obese patient.

Our study had a number of limitations. The follow-up time for this group was relatively short, only 23 months, which may have contributed to the low overall recurrence rate of 12%. The pathologic data on stage, margin status, extracapsular extension, and lymph node involvement were not available to correlate with the outcomes. This is particularly important considering that recurrence in obese patients may be related to the technical difficulties of performing optimal prostate resection and lymph node dissection. As a cohort receiving RP as a primary therapy, this patient population was subject to a surgical selection bias that may select for low-risk patients. Our definition of BMI compared with other definitions seeking to quantify obesity, such as lean body mass and waist/hip ratio, may not be the most accurate method of assessing obesity. Finally, African Americans are relatively underrepresented in CaPSURE compared with the national census data. This has particular relevance when comparing these results to the results of other databases such as the Center for Prostate Cancer Research and Shared Equal Access Regional Center Hospital Database Study Group, which represent a greater proportion of African Americans.

CONCLUSIONS

The results of our study have demonstrated that obesity is an independent predictor of disease recurrence in community-based patients undergoing RP. Because of both increased comorbidities and greater rates of recurrence, obese individuals undergoing RP require vigilant follow-up care. Continued research is necessary to evaluate the efficacy of other treatments in obese patients with prostate cancer, as well as to clarify how prostate cancer recurrence affects survival in obese patients.

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