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Impact of Body Mass Index on Biochemical Recurrence Rates After Radical Prostatectomy: An Analysis Utilizing Propensity Score Matching

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Abstract

OBJECTIVES—To investigate the significance of body mass index (BMI) as an independent predictor of biochemical recurrence in men treated with surgery for clinically localized adenocarcinoma of the prostate.

METHODS—A total of 1877 obese patients who underwent radical prostatectomy were matched to overweight and normal-weight patients in a 1:1 ratio on the basis of propensity scores. This resulted in an overall study population of 5631 men. Clinicopathologic characteristics and biochemical recurrence outcomes after surgery were compared between the three BMI cohorts.

RESULTS—Normal-weight patients exhibited lower-grade disease compared with overweight and obese patients ($P = 0.021$). Lower BMI was also significantly associated with lower rates of positive surgical margins ($P < 0.001$) and extraprostatic extension ($P < 0.001$). Body mass index was not associated with lymph node involvement ($P = 0.226$) or seminal vesicle invasion ($P = 0.142$). Body mass index, age, biopsy Gleason score, preoperative prostate-specific antigen level, and clinical tumor stage were independent predictors of biochemical recurrence ($P < 0.001$).

CONCLUSIONS—Propensity score–based matched analyses indicate that higher BMI is associated with adverse pathologic findings and is a strong independent predictor of biochemical recurrence after radical prostatectomy. These results support the hypothesis that inherent differences may exist in the biological properties of prostate cancer in obese men compared with normal-weight men. Therefore, BMI is an important criterion to consider during subsequent decision making and counseling of patients with prostate cancer.

The prevalence of overweight and obese individuals is increasing dramatically in most regions of the world and is now considered the primary cause of morbidity and mortality in the United States.¹ Obesity is associated with a number of chronic diseases, such as diabetes, coronary artery disease, and hypertension.² From 2003 to 2004, approximately 17% of American children and adolescents were overweight, and 32% of adults were obese.³ Although the effect of excessive body weight on cardiovascular disease and cancer are well established, data regarding the relationship between weight and cancer outcomes are limited.^{4,5} Obesity has been consistently associated with cancers of the endometrium, kidney, gallbladder, breast, and colon.⁶ Data regarding the relationship between obesity and risk of prostate cancer are sparse and inconsistent. Some investigators suggest a higher risk

for prostate cancer, whereas others have demonstrated the opposite association in large prospective studies.⁷⁻⁹

Several studies investigating the association between obesity, pathologic characteristics, and biochemical recurrence after radical prostatectomy (RP) have been published, with conflicting results.¹⁰⁻¹³ Nevertheless, it has been suggested that increased body weight is associated with worse clinical outcomes after RP.¹⁴ It has been proposed that this association is the result of a link between increasing body mass index (BMI) and the intrinsic biologic properties of prostate cancer in obese patients.^{15,16} If BMI, however, is unrelated to tumor biology, more severe disease and worse outcomes in obese patients should be considered a result of factors other than body weight. In previous retrospective studies that have examined the influence of BMI on biochemical recurrence rates after RP, obese patients underwent surgery more recently simply because of the increased prevalence of obesity in recent years. One limitation of prior studies is the fact that more recent year of surgery was concomitant with migration toward earlier-stage disease at the time of radical prostatectomy, resulting from advances in improved screening and earlier detection of prostate cancer.¹⁷ Furthermore, this stage migration has been accompanied by a decline in patient age and preoperative prostate-specific antigen (PSA) levels.¹⁸ These trends in prostate cancer patients over time substantially limit the statistical value of comparing outcomes of overweight and obese patients with those of normal-weight patients, especially when pathologic data are analyzed without adjusting for confounding factors.

Appropriate matching of patients among different BMI cohorts may lead to a better understanding of the true significance of BMI as a prognostic indicator for disease severity and outcomes after RP. To date no studies have used propensity score matching to examine whether BMI is an independent prognostic variable for predicting postoperative tumor stage and biochemical outcomes after surgery. We investigated the significance of BMI as a predictor of biochemical recurrence in men undergoing RP by utilizing propensity score matching to adjust for multiple preoperative variables.

MATERIAL AND METHODS

Between 1984 and 2006, more than 14,800 men underwent RP for clinically localized adenocarcinoma of the prostate at our institution. Information regarding BMI was available for 12,804 patients. Patients treated with neoadjuvant hormonal therapy (n = 196), clinical stage T1a or T1b disease (n = 173), and incomplete preoperative information including preoperative PSA level (n = 381), clinical stage (n = 32), biopsy Gleason score (n = 29), and race (n = 38) were excluded. This resulted in a population of 11,790 patients, who were then stratified according to BMI as normal weight (BMI less than 25 kg/m², n = 3365), overweight (BMI 25 to 29.9 kg/m², n = 6548), and obese (BMI 30 or more kg/m², n = 1877).

Patients in the normal-weight and overweight cohorts were matched 1:1 to the cohort of obese patients on the basis of propensity scores. Therefore, a total of 5631 men formed the overall study population. A subset (n = 2796) of the 14,800 patients has been previously analyzed but not in a matched fashion.¹⁴ Data for our study were obtained and analyzed according to an approved institutional review board protocol.

Propensity scores were used to match members of the three BMI cohorts according to a range of characteristics, as previously described.^{19,20} Propensity scores were calculated for each patient using multivariable logistic regression according to the following covariates: age, preoperative PSA level, year of surgery, biopsy Gleason score, and clinical tumor stage. This method is an approach to control for imbalances in confounding factors among discrete

study cohorts. Continuous and categorical factors are combined to yield a propensity score for each individual in the study population, then individuals in each of the different study cohorts are matched to those in the reference cohort on the basis of their calculated propensity scores. The greatest advantage of implementing this method of matching is that variables are weighted by their relative importance rather than being assigned equal weights. Furthermore, it has been shown that cohort means and standard deviations related to covariates used for matching are equivalent when composite propensity scores are matched. Matching was performed with a computer application implemented in SPSS by Painter to select for the most similar propensity scores across each of the different BMI strata in a 1:1 ratio with respect to the reference group of patients who were obese.

We compared the clinical and pathologic characteristics of the three BMI cohorts using chi-square test for categorical and one-way analysis of variance for continuous variables. Patient age, preoperative PSA values, and year of surgery were evaluated as continuous variables. Clinical stage, biopsy, and prostatectomy Gleason score (6 or less, 7, 8 to 10), and race (white or black) were considered categorical variables. Pathologic stage was treated as a single variable categorized into organ-confined status, extraprostatic extension, and seminal vesicle and lymph node involvement, with each category mutually exclusive.

The time to PSA recurrence was compared among groups by a Cox proportional hazards model with forward stepwise selection. The actuarial risk of PSA recurrence was calculated with the Kaplan-Meier method and compared across the three BMI cohorts with the log-rank test. All statistical analyses were performed with SPSS 13.0 (SPSS, Chicago, Ill).

RESULTS

Clinical and pathologic characteristics of the three matched study cohorts are shown in Table 1. Overall mean follow-up ($\pm$ standard deviation) was 4.5 ± 3.8 years for the entire cohort of patients. Mean follow-up was 4.7 ± 3.9 , 4.6 ± 3.8 , and 4.3 ± 3.7 years for normal-weight, overweight, and obese patients, respectively. There were no statistically significant differences with respect to the variables used for propensity score matching, including patient age at the time of surgery ($P = 0.988$), preoperative PSA level ($P = 0.204$), median year of surgery ($P = 0.830$), biopsy Gleason score ($P = 0.765$), and clinical tumor stage ($P = 0.880$). These results indicate that the three different BMI patient cohorts were well matched with respect to established preoperative variables.

Examination of postoperative variables, including prostatectomy Gleason score, demonstrated significant differences across BMI cohorts. Normal-weight patients exhibited higher rates of lower-grade disease ($P = 0.021$) compared with overweight and obese patients. Lower BMI was also significantly associated with lower rates of positive surgical margins ($P < 0.001$). Higher BMI was statistically associated with worse pathologic stage ($P < 0.001$). Furthermore, normal-weight patients demonstrated significantly lower prostate specimen weight after RP than overweight and obese patients ($P < 0.001$).

Table 2 demonstrates the association of preoperative variables with biochemical recurrence. In univariate proportional hazards analysis, BMI ($P < 0.001$), patient age ($P < 0.001$), race ($P = 0.001$), biopsy Gleason score ($P < 0.001$), preoperative PSA level ($P < 0.001$), clinical stage ($P < 0.001$), and year of surgery ($P < 0.001$) were all predictive of biochemical recurrence after RP. In multivariable analysis, only BMI cohort ($P < 0.001$), age ($P < 0.001$), biopsy Gleason score ($P < 0.001$), preoperative PSA level ($P < 0.001$), and clinical tumor stage ($P < 0.001$) remained predictive of biochemical recurrence after surgery.

Kaplan-Meier analysis demonstrated overall 5- and 10-year biochemical recurrence-free survival rates of 87% and 77%, respectively, for all patients included in this study (data not

shown). In stratified analyses, normal-weight, overweight, and obese patients had 5- and 10-year biochemical recurrence-free survival rates of 90% and 82%, 84% and 77%, and 78% and 63%, respectively (Fig. 1). Time to biochemical recurrence after surgery differed significantly across the three BMI cohorts (log-rank P value <0.001).

Table 3 depicts univariate and multivariable proportional hazards analyses predicting biochemical recurrence for preoperative and postoperative characteristics combined. Univariate analyses showed significant associations between prostatectomy Gleason sum ($P < 0.001$), pathologic stage ($P < 0.001$), and positive surgical margin status ($P < 0.001$) with postoperative biochemical recurrence. In multivariable analyses, BMI cohort ($P = 0.001$), preoperative PSA level ($P < 0.001$), year of surgery ($P = 0.007$), prostatectomy Gleason sum ($P < 0.001$), pathologic stage ($P < 0.001$), and surgical margin status ($P < 0.001$) remained independent predictors of biochemical recurrence.

COMMENT

It is widely accepted that there has been a dramatic stage migration among men with prostate cancer since PSA screening was introduced in the late 1980s.²¹ An increasing number of men are now being diagnosed at a younger age with more favorable clinicopathologic characteristics, which makes it necessary to control for these variables by using either multivariable regression, matching, or a combination thereof. By matching patients for preoperative variables, including age, clinical stage, PSA level, biopsy Gleason score, and year of surgery, the effect of BMI on pathologic features after RP can be evaluated in more detail.

We have demonstrated that overweight and obese patients are significantly more likely to exhibit adverse pathologic features and consequently worse biochemical recurrence rates after RP compared with normal-weight patients. To our knowledge, we have examined the largest cohort of patients thus far ($n = 5631$), investigating the relationship between BMI and biochemical recurrence using propensity score matching for control of other prognostic factors. Our data support the hypothesis that BMI is a strong independent predictor of biochemical recurrence after RP, with obese patients having worse outcomes.

Basset *et al.*²² showed that BMI was an independent predictor of biochemical recurrence in multivariable Cox regression analysis. This is in agreement with our findings; however, when BMI was stratified into six categories, no overall P value was reported. Furthermore, they did not adjust for pathologic variables in their analysis and focused more on preoperative data and comorbidities. A previous study by Freedland *et al.*²³ showed that with the exception of positive surgical margins, the association between obesity and adverse outcomes was strongest among men treated in the last 10 years.

In an earlier study using the Shared Equal Access Regional Cancer Hospital (SEARCH) Database, obesity was found to be related to year of surgery and race.¹³ An association between obesity and higher-grade tumors and a trend between obesity and increased risk of positive surgical margins as well as higher biochemical failure rates was also observed. This is consistent with our findings of a higher percentage of high-grade tumors, higher rates of extraprostatic extension, and higher rates of positive surgical margins in obese patients. The hazard ratios (HRs) for biochemical recurrence of overweight (HR = 0.90) and mildly obese patients (HR = 1.19) did not differ significantly from the HR for normal-weight patients. Freedland *et al.* found the biggest difference between normal-weight and moderately and severely obese patients (HR = 1.99). In the present study we did not differentiate between obese and severely obese patients. After adjusting for surgeon in the multivariable Cox regression analysis, overweight was no longer an independent predictor of biochemical

recurrence (data not shown). However, overall BMI and obesity remained independent predictors of worse biochemical recurrence outcomes.

One limitation that may affect our study is selection bias, because we did not include potential comorbidities in our analyses. Obese patients are more likely to have comorbidities (eg, diabetes, hypertension, and vascular disease) that may influence biochemical recurrence rates. There are a number of hypotheses to explain the association between obesity, higher risk of high-grade prostate cancer, and prostate cancer progression. Alterations in hormone levels, such as estrogen, testosterone, insulin, insulin-like growth factor I, leptin, and adiponectin, or lifestyle factors have been reported to influence disease stage, grade, and biochemical recurrence rates in obese patients.^{24,25} However, it is challenging to investigate BMI as an independent factor, because it is frequently associated with conditions (eg, smoking, high-fat diet, and diabetes) that are known to negatively impact cancer outcomes.^{21,22} Another limitation of our study is that we did not include these important confounding factors in our analyses. Information regarding lifestyle factors or serum samples to investigate hormonal levels was not available.

CONCLUSIONS

We used propensity score matching to investigate the association between BMI and clinicopathologic outcomes after RP in a large cohort of patients. Elevated BMI was associated with statistically significant higher Gleason grade, higher rates of extraprostatic extension, and higher rates of positive surgical margins. Increased BMI was also a strong independent predictor of biochemical recurrence after radical prostatectomy. Therefore, BMI is an important criterion to consider during clinical decision making and counseling patients for management of prostate cancer.

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Figure 1. Kaplan-Meier actuarial likelihood of biochemical recurrence (PSA $\geq$ 0.2 ng/ml) following radical prostatectomy for normal weight, overweight, and obese patients.

Table 1

Clinicopathologic characteristics of prostate cancer patients undergoing radical prostatectomy

Characteristic	BMI Grouping			P Value*
	Normal Weight	Overweight	Obese	
Patients (n)	1877	1877	1877	
Follow-up mean $\pm$ SD (yr)	4.7 $\pm$ 3.9	4.6 $\pm$ 3.8	4.3 $\pm$ 3.7	0.023 (ANOVA)
Median year of surgery	1999	1999	1999	0.830 (ANOVA) [†]
Age (yr)				0.988 (ANOVA) [†]
Median (range)	57 (33–75)	57 (37–74)	57 (35–73)	
Mean $\pm$ SD	56.8 $\pm$ 6.8	56.8 $\pm$ 6.2	56.8 $\pm$ 6.2	
Race, n (%)				<0.001
White	1786 (95)	1753 (94)	1684 (90)	
Black	87 (5)	119 (6)	189 (10)	
PSA level (ng/mL)				0.204 (ANOVA) [†]
Median (range)	5.7 (0.2–79.0)	5.7 (0.1–64.8)	5.7 (0.1–66.0)	
Mean $\pm$ SD	7.0 $\pm$ 5.7	6.9 $\pm$ 5.0	7.1 $\pm$ 5.6	
PSA density (ng/mL/cm ³)				0.058 (ANOVA) [†]
Median (range)	8.8 (0.1–215)	9.1 (0.7–520)	9.2 (0.9–436)	
Mean $\pm$ SD	11.4 $\pm$ 12.1	12.7 $\pm$ 19.2	12.2 $\pm$ 17.3	
Clinical stage, n (%)				0.880 [†]
cT1	1248 (67)	1229 (66)	1218 (65)	
cT2	616 (33)	633 (34)	645 (34)	
cT3	13 (0.7)	15 (0.8)	14 (0.7)	
Prostate weight (g)				<0.001 (ANOVA)
Median (range)	49 (9–224)	52 (7–254)	52 (13–235)	
Mean $\pm$ SD	52 $\pm$ 17	55 $\pm$ 20	57 $\pm$ 22	
Biopsy Gleason score, n (%)				0.765 [†]
2–6	1434 (76)	1419 (76)	1402 (75)	
7	377 (20)	393 (21)	401 (21)	
8–10	66 (4)	65 (4)	74 (4)	
Prostatectomy Gleason score, n (%)				0.021
2–6	1223 (65)	1166 (62)	1133 (60)	
7	555 (30)	607 (32)	616 (33)	
8–10	99 (5)	104 (6)	128 (7)	
Pathologic stage, n (%)				<0.001
Organ-confined disease	1323 (70)	1234 (66)	1139 (61)	
Extraprostatic extension	454 (24)	506 (27)	612 (33)	
Seminal vesicle invasion	52 (3)	89 (5)	76 (4)	
Lymph node invasion	43 (2)	44 (2)	46 (3)	
Positive surgical margin, n (%)	208 (11)	249 (13)	337 (18)	<0.001

BMI = body mass index; ANOVA = analysis of variance; PSA = prostate-specific antigen.

* Indicates test for comparison among the three BMI cohorts. All tests are chi-squared, unless stated otherwise.

[†] Indicates matched variable.

Table 2

Univariate and multivariable proportional hazards regression models of preoperative clinical variables predicting biochemical recurrence after radical prostatectomy

Variable	Univariate Analyses			Multivariable Analyses		
	HR	95% CI	P Value	HR	95% CI	P Value
BMI (relative to normal weight)			<0.001			<0.001
Overweight	1.31	1.02–1.69		1.30	1.01–1.68	
Obese	2.04	1.61–2.58		1.91	1.51–2.44	
Age	1.04	1.02–1.05	<0.001	1.03	1.01–1.04	<0.001
Race (black vs. white)	1.72	1.25–2.37	0.001	1.31	0.95–1.82	0.102
Biopsy Gleason score			<0.001			<0.001
7 vs. 2–6	3.90	3.17–4.81		2.84	2.29–3.54	
8–10 vs. 2–6	9.95	7.61–12.99		6.06	4.56–8.06	
Preoperative PSA level	1.06	1.05–1.07	<0.001	1.05	1.04–1.06	<0.001
Clinical stage (relative to T1)			<0.001			<0.001
T2	2.47	2.02–3.01		1.86	1.50–2.30	
T3	8.19	5.08–13.19		2.51	1.48–4.24	
Year of surgery	0.94	0.91–0.96	<0.001	0.99	0.97–1.03	0.945

HR = hazard ratio; CI = confidence interval; BMI = body mass index; PSA = prostate-specific antigen.

Table 3

Univariate and multivariable proportional hazards regression models of clinical and pathological variables predicting biochemical recurrence after radical prostatectomy

Variable	Univariate Analyses			Multivariable Analyses		
	HR	95% CI	P Value	HR	95% CI	P Value
BMI (relative to normal weight)			<0.001			0.001
Overweight	1.31	1.02–1.69		1.15	0.89–1.49	
Obese	2.04	1.61–2.58		1.53	1.20–1.96	
Age	1.04	1.02–1.05	<0.001	1.01	0.99–1.03	0.129
Race (black vs. white)	1.72	1.25–2.37	0.001	1.31	0.94–1.81	0.105
Preoperative PSA level	1.06	1.05–1.07	<0.001	1.02	1.01–1.03	<0.001
Year of surgery	0.94	0.91–0.96	<0.001	1.04	1.01–1.06	0.007
Prostatectomy GS (relative to GS 2–6)			<0.001			<0.00
GS 7	6.64	5.10–8.65		3.41	2.57–4.54	
GS 8–10	21.0	15.68–28.12		7.11	5.09–9.93	
Pathological stage (relative to organ confined)			<0.001			<0.001
Extraprostatic extension	5.85	4.46–7.68		2.93	2.18–3.93	
Seminal vesicle invasion	19.26	13.78–26.93		5.57	3.82–8.12	
Lymph node invasion	33.74	24.52–46.43		9.23	6.30–13.48	
Positive surgical margins	4.64	3.81–5.65	<0.001	1.99	1.61–2.48	<0.001

GS = Gleason sum. Other abbreviations as in Table 2.