Obesity, Weight Gain, and Risk of Biochemical Failure among Prostate Cancer Patients following Prostatectomy

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Abstract

Purpose: Several lines of evidence suggest that diet and weight gain may be important environmental factors implicated in prostate carcinogenesis, especially in tumor progression. The purpose of this study was to evaluate obesity at different ages in a well-characterized cohort of prostate cancer patients treated with prostatectomy and to develop a prognostic model that incorporates body mass index (BMI) as a measure of obesity.

Experimental Design: We carried out a prospective study of 526 patients registered at the M.D. Anderson Cancer Center from 1992 to 2001. Kaplan-Meier and Cox proportional hazard analyses were done.

Results: During an average follow-up of 54 months, 97 (18%) post-prostatectomy patients experienced biochemical failure. Patients who were obese (BMI $\geq$ 30 kg/m^2) at diagnosis had a higher rate of biochemical failure than nonobese men (P = 0.07). Those obese at 40 years had an even greater rate of biochemical failure (P = 0.001). Higher BMI at diagnosis [hazard ratio (HR), 1.07; P = 0.01] and Gleason score = 7 (4 + 3) and $\geq$8 (HR, 3.9; P = 0.03 and HR, 10.0; $P \leq 0.001$, respectively) remained significant independent predictors of biochemical failure in multivariate analysis. Men who gained weight at the greatest rate (>1.5 kg/y) between 25 years and diagnosis progressed significantly sooner (mean time, 17 months) than those who exhibited a slower weight gain (mean time, 39 months; P_{trend} = 0.005). The inclusion of obesity to the clinical nomogram improved performance.

Conclusions: Our findings validate the importance for a role of obesity in prostate cancer progression and suggest a link to the biological basis of prostate cancer progression that can be therapeutically exploited.

Prostate-specific antigen (PSA) screening has resulted in the increased detection of patients with localized prostate cancer. Men diagnosed with clinically organ-confined tumors are often confronted with a therapeutic dilemma. For some, the disease may not be life threatening; for others, radiation or surgery are curative, whereas a proportion will experience further progression despite adequate local therapy. Whereas there are algorithms to predict risk of progression following surgery (1, 2), most nomograms in clinical use include only traditional tumor-specific criteria (grade, stage, and PSA) to predict recurrence. Post-therapy, a rising serum PSA serves as a surrogate of meaningful recurrence. The long-range goal of such nomograms and prediction tables is to provide a more refined tool to allow patients and physicians to make informed decisions regarding therapy.

Furthermore, existing nomograms do not provide a link to the biology of prostate cancer progression. Incorporating factors mechanistically linked to carcinogenesis should improve performance of the predictive nomograms and also provide insight into the biology of progression. Such knowledge may also lead to new treatments targeting specific pathways implicated in progression.

There are several lines of evidence to suggest that diet and weight gain may be important environmental factors implicated in prostate carcinogenesis. Experimental observations suggest that energy balance, as reflected in obesity, affects sex steroid, insulin, and insulin-like growth factor-I pathways, which in turn modulate prostate cancer progression (3, 4). In addition, two recent retrospective studies suggest that obesity plays a role in biochemical failure (5, 6). The purpose of this study was to develop a prognostic model that incorporates measures of obesity. To achieve this goal, we evaluated self-reported measures of obesity at different ages in a well-characterized cohort of prostate cancer patients treated with radical prostatectomy.

Patients and Methods

Patient population. The study subjects included patients with histologically confirmed adenocarcinoma of the prostate who registered at The University of Texas M.D. Anderson Cancer Center between 1991

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and 2001. These patients were drawn from a series of 997 patients enrolled in epidemiologic studies in the Department of Epidemiology at the M.D. Anderson Cancer Center treated with different modalities. Men with a previous history of invasive cancer were excluded from these studies. There were 526 patients who had prostatectomy as their definitive treatment, after excluding those who had received neoadjuvant or adjuvant therapy (n = 151). As previously described (7), after written informed consent was obtained, each participant donated 10 mL of blood and completed a personal interview that assessed demographic data, risk factor information, and family history of cancer.

Patient characteristics. Among the 526 patients included in the analysis, 405 were non-Hispanic White, 49 were Hispanic, and 72 were African American. Self-reported ethnicity and race information were collected during personal interview. All Hispanic patients identified themselves as being of White race. Clinical and pathologic information (e.g., Gleason score, pathologic stage, and pretreatment PSA) and follow-up data were obtained by chart review and from the pathology database. Because clinicopathologic features were similar between Hispanic and non-Hispanic Whites, these groups were combined in the analyses. Patients who did not return to the institution (n = 40) for their regular follow-up were contacted by telephone to update their health status and most recent PSA results. According to institutional practice, biochemical failure is defined as a serum PSA level of ≥0.1 ng/mL, measured by the Tosoh immunometric assay (Tosoh, San Francisco, CA) following surgery.

Body mass index and weight gain calculation. Body mass index (BMI, kg/m^2) was calculated from self-reported weight and height at ages 25, 40, and at prostate cancer diagnosis. BMI was analyzed both as a continuous variable and categorized according to current National Heart, Lung, and Blood Institute guidelines. Because there were no patients considered to be underweight, three categories were used (BMI: normal, 18.5-24.9 kg/m^2; overweight, 25-29.9 kg/m^2; and obese, ≥30.0 kg/m^2). Annualized average weight change between age 25 and diagnosis was calculated by averaging the total weight gained or lost over the years between age 25 and age at diagnosis.

Statistical analysis. χ^2 tests or Fisher's exact tests were used to examine differences in the distribution of the clinical prognostic factors and obesity categories to compare cases whose disease progressed and those whose disease did not progress. Pathologically, tumors were classified as pT2 (organ confined) and pT3 (extraprostatic extension +/− seminal vesicle invasion). Gleason score was analyzed in four categories [≤6, 7 (3 + 4), 7 (4 + 3), and ≥8]. Due to the skewed distribution, presurgical PSA values were log-transformed and analyzed continuously. Kruskal-Wallis tests were used to evaluate differences in means for continuous variables between groups. Time to progression was measured from date of prostatectomy until the date of first PSA of ≥0.1 ng/mL or censored at the time of last normal PSA test. The progression-free survival rate was estimated using the Kaplan-Meier method with the log-rank test used to determine statistical significance. Univariate Cox proportional hazard regression models evaluating each potential risk factor individually were conducted to evaluate the crude effect of each variable on risk of biochemical failure. To estimate the independent effects of variables of interest, we fit multivariate Cox proportional hazard models incorporating significant clinicopathologic

Table 1. Patient characteristics

Variable	Normal (n = 128)	Overweight (n = 267)	Obese (n = 131)	P*
Age (mean ± SD)	60.8 ± 7.3	59.7 ± 7.1	58.9 ± 7.0	0.06†
Ethnicity				
White/Hispanic	113 (88.3)	232 (86.9)	109 (83.2)	0.46
African American	15 (11.7)	35 (13.1)	22 (16.8)	
Pathologic stageT3/T4	29 (22.7)	72 (27.0)	38 (29.2)	0.47
Surgical margin positive	19 (15.0)	34 (12.8)	24 (18.6)	0.31
Seminal vesicle involvement	10 (7.8)	19 (7.1)	18 (13.8)	0.08
Lymph node positive	4 (3.1)	8 (3.0)	2 (2.3)	0.91
Preoperative PSA >10 ng/mL	31 (24.6)	51 (19.2)	30 (23.1)	0.43
Gleason score				
≤6	34 (26.6)	64 (24.1)	33 (25.4)	0.94
7(3 + 4)	40 (31.3)	84 (31.6)	47 (36.2)	
7(4 + 3)	28 (21.9)	57 (21.4)	25 (19.2)	
≥8	26 (20.3)	61 (22.9)	25 (19.2)	
Mean years of education	15.4	15.0	14.6	0.18†
Physical activity				
≥1 times/wk	100 (79.4)	196 (75.1)	83 (64.3)	0.04
Few times/mo	12 (9.5)	26 (10.0)	14 (10.9)	
Rarely/never	14 (11.1)	39 (14.9)	32 (24.8)	
Positive family history	28 (21.9)	58 (21.7)	28 (21.4)	0.99
Smoking status				
Current	16 (12.5)	26 (9.7)	9 (6.9)	0.13
Former	69 (53.9)	135 (50.6)	82 (63.1)	
Never	43 (33.6)	106 (39.7)	39 (30.0)	
Disease status				
No progression	104 (81.3)	223 (83.5)	102 (77.9)	0.39
Progression	24 (18.8)	44 (16.5)	29 (22.1)	

*χ^2, P.
†Kruskal-Wallis test P.

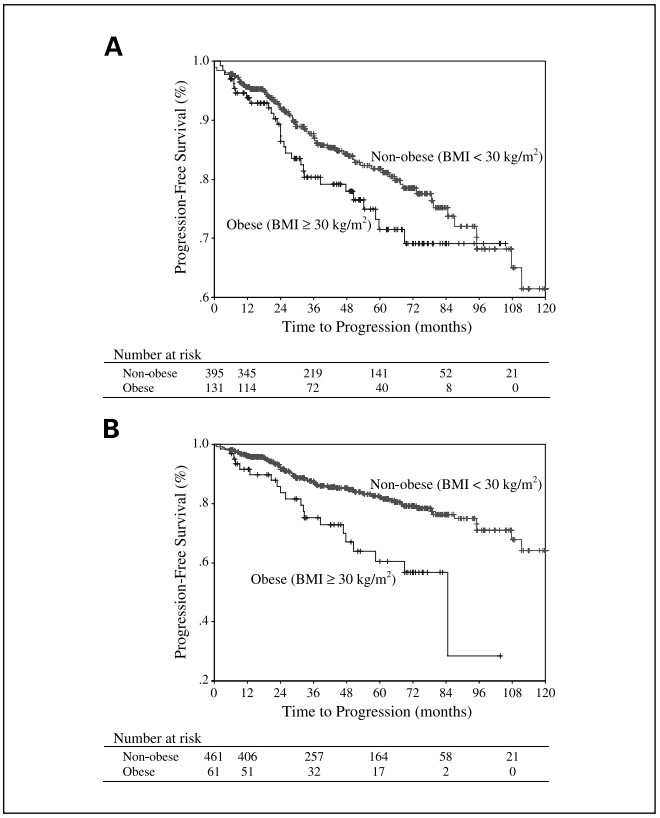

Fig. 1. *A*, Kaplan-Meier analysis of time to biochemical failure in patients by obesity at time of diagnosis (log-rank test, $P = 0.007$). *B*, Kaplan-Meier analysis of time to biochemical failure in patients by obesity at age 40 (log-rank test, $P = 0.001$).

variables and BMI. We developed independent models with BMI at age 40 as well as at time of diagnosis; BMI was modeled both continuously and categorically, dichotomized by obesity (≥30 kg/m^2).

Development and evaluation of clinical nomograms. Nomograms were generated based on the multivariate Cox models with or without BMI at diagnosis. Receiver operating characteristic curve analyses were done to compare the nomogram-predicted 5-year progression-free survival probability with the actual follow-up data. The areas were calculated by using 100 bootstrap samples from the original 526 patients modeled for the nomogram. As noted by Harrell, although "indexes such as *c* (concordance) are widely applicable and easily interpretable, they are not sensitive" for detecting small differences between two models (8). Therefore, we used a more sensitive likelihood-ratio test to detect differences in discrimination ability between two models (8). Statistical analyses were done using the S-Plus and the SPSS softwares. Research supported by National Cancer Institute grants CA84964, CA90270, NIEHS ES07784, and Department of Defense grant DAMD 17-98-1-8471.

Results

Relationship of clinical characteristics, obesity, and lifestyle characteristics to biochemical failure. The mean age at diagnosis of the 526 patients was 60 years (range, 39-73) and follow-up averaged 54 months (range, 6-120 months). Biochemical failure was documented in 97 (18%) patients (18% among Whites and 21% among African Americans). As expected, patients whose prostate cancer progressed were more likely to have more advanced disease (higher stage tumors, positive surgical margins, seminal vesicle invasion, positive lymph nodes, and preoperative PSA of >10 ng/mL) than those whose did not progress (data not shown). Table 1 compares the clinical and lifestyle characteristics by National Heart, Lung, and Blood Institute BMI category. Obese patients were younger at time of diagnosis and a larger percentage of them reported to rarely or never engaging in routine physical activity compared with the rest of the patients. There were no significant differences in ethnicity, clinical characteristics, family history, and smoking status in obese compared with nonobese men. As expected, the number of obese men increased with age from 2% at age 25, to 12% at age 40, to 25% at time of diagnosis. Men who experienced biochemical failure were similar in height to men whose prostate cancer did not progress; however, they were heavier and had statistically significant higher mean BMIs at age 25 (24.0 versus 23.3 kg/m^2, respectively), age 40 (26.7 versus 25.6 kg/m^2, respectively), and at diagnosis (28.5 versus 27.6 kg/m^2, respectively). In our study population, we found no differences in mean BMI at diagnosis by year of prostatectomy (data not shown).

Obesity and time to biochemical failure. Biochemical failure–free survival was estimated using the Kaplan-Meier method by obesity at diagnosis and at age 40 (Fig. 1A and B). Patients who were obese at time of diagnosis had marginally significant higher rates of PSA failure over time than nonobese men ($P = 0.07$). At 5 years after surgery, 71.5% of obese patients were recurrence free compared with 81.7% of nonobese men. When comparing patients by obesity at 40 years of age, obese men had statistically significant lower biochemical failure–free survival ($P = 0.001$) than nonobese patients. There was no difference in the follow-up time between these two groups (mean, 53.3 versus 54.6 months, respectively; $P = 0.7$). Because patients have been diagnosed over a 12-year period, we analyzed the data by year of diagnosis and found no difference in the risk of biochemical failure. Using Cox proportional hazards models, risk factors were evaluated as potential prognostic indicators by univariate analysis (Table 2). As expected, we found the traditional clinicopathologic variables [e.g., preoperative PSA (HR, 1.86), advanced pathologic stage (HR, 4.83), Gleason score both 7(4 + 3); HR, 5.04 and ≥8; HR, 17.47, and being African American (HR, 1.79) to be strong predictors of biochemical failure; Table 2]. Obesity at ages 25 (HR, 2.31) and 40 (HR, 2.35) and annual weight gain of >1.5 kg/y between age 25 to diagnosis (HR, 2.32) were also associated with significantly increased risk of biochemical failure. A small number of men lost weight between age 25 and diagnosis ($n = 36$); however, their risk of biochemical failure was not different relative to men who gained weight (16% versus 19%, $P = 0.4$; data not shown). Family history and physical activity were not associated with risk of progression. In the final multivariate model, after simultaneous adjustment for relevant variables (Table 2), Gleason score at prostatectomy = 7 (4 + 3) (HR, 3.89) and ≥8 (HR, 10.00) and BMI at diagnosis (HR, 1.07) remained as independent predictors for biochemical failure. We found that modeling BMI as a continuous variable, explained a greater proportion of the variance in the data than using it as a dichotomized variable (i.e., obese compared with nonobese).

To assess the prognostic value of obesity at diagnosis, we explored mean time to progression for obese and nonobese subjects (Table 3). Men who were obese at diagnosis experienced biochemical failure sooner than normal weight

men (mean time, 26.6 versus 36.9 months), although the trends were not statistically significant. We observed a statistically significant association between time to progression and average annual weight change between age 25 and diagnosis. Men who gained weight at the greatest rate (>1.5 kg/y) progressed significantly sooner (mean time, 16.7 months) than those who exhibited slower weight gain annually (mean time, 23.7 months) or those with almost no weight gain (mean time, 39.0 month; $P_{trend} = 0.005$).

Influence of obesity on the performance of clinical nomogram. Based on the multivariate Cox analysis, we developed two nomograms, one including only clinicopathologic characteristics (Fig. 2A) and the other including the same variables plus BMI at diagnosis (Fig. 2B). The likelihood ratios for the above two models were 88.0 (model without BMI at diagnosis) and 94.6 (model with BMI at diagnosis) which resulted in a $P = 0.02$ based on a χ^2 test with 1 degree of freedom. These results indicate that the nomogram incorporating BMI is a better predictor of biochemical failure in this population. This nomogram can be used in a clinical setting to determine the 5-year progression-free probability for individual patients. For example, using Fig. 2A, a preoperative PSA value of 10 contributes 17 points that is determined by drawing a line from the PSA to the corresponding location on the "points" scale. In the same way, points are assigned for all other variables and added together. Based on the total number of points, the 5-year progression-free probability is determined by finding the corresponding location on the probability scale. Using the nomogram without BMI (Fig. 2A) for a patient with a PSA of 10, a Gleason score of 7 (4 + 3), prostatic capsular invasion and negative surgical margins, seminal vesicle invasion, and lymph nodes, the probability of being progression-free 5 years after surgery is ~82%. In comparison, using the nomogram incorporating BMI (Fig. 2B), the probability of remaining free of disease at 5 years varies by BMI. For a normal weight patient (BMI = 25 kg/m^2), the 5-year free recurrence probability is 84% compared with 72% for a patient with the same clinical characteristics but who is obese (BMI = 32 kg/m^2).

Discussion

Our data show that obese patients with prostate cancer are at an increased risk of biochemical failure following prostatectomy. Furthermore, the inclusion of obesity into a widely used nomogram improves its performance. These findings support the hypothesis that increased obesity is an important independent prognostic variable for patients with clinically localized prostate cancer. Although the association between obesity and risk of several cancers is well established, its role in the natural history of prostate cancer, based on epidemiologic studies, is

Table 2. Univariate and multivariate Cox proportional hazard analyses

Variable	Univariate HR (95% confidence interval)	Multivariate HR (95% confidence interval)
Age (continuous)*	0.98 (0.96-1.01)	
African American versus Whites	1.79 (1.01-3.16)	
Log (preoperative PSA), ng/mL	1.86 (1.42-2.45)	1.12 (0.80-1.57)
Gleason score		
≤6	1.00	1.00
7(3 + 4)	2.25 (0.72-7.05)	2.10 (0.57-7.74)
7(4 + 3)	5.04 (1.73-14.72)	3.89 (1.11-13.68)
≥8	17.47 (6.34-48.11)	10.00 (2.87-34.88)
Pathologic stage, T3 (versus T1/T2)*	4.83 (3.16-7.39)	
Extraprostatic extension (versus organ confined)	4.47 (2.89-6.91)	1.70 (0.96-3.02)
Seminal vesicle invasion, yes (versus no)	5.46 (3.52-8.47)	1.52 (0.86-2.70)
Positive surgical margins (versus negative)	3.04 (1.96-4.72)	1.49 (0.91-2.45)
Lymph node positive (versus negative)	4.58 (2.21-9.47)	1.57 (0.66-3.73)
Positive family history (versus negative)*	1.54 (0.99-2.41)	
Obese at age 25 (versus nonobese)*	2.31 (1.01-5.30)	
Obese at age 40 (versus nonobese)*	2.35 (1.43-3.86)	
Obese at diagnosis (versus nonobese)*	1.41 (0.91-2.18)	
BMI at diagnosis (continuous)	1.07 (1.02-1.12)	1.07 (1.02-1.13)
Weight change age 25 to diagnosis (continuous)*	1.62 (1.00-2.61)	
Weight change age 25 to diagnosis* (kg/y)		
Gain, <0.5	1.00	
Gain, 0.5-1.5	1.05 (0.66-1.69)	
Gain, >1.5	2.32 (1.06-5.08)	
Physical activity*		
≥1 times/wk	1.00	
Few times/mo	1.12 (0.57-2.17)	
Rarely/never	0.90 (0.51-1.58)	

*Dropped from multivariate model.

Table 3. Time to biochemical failure by obesity and weight change among 97 patients

Variable	*n*	Mean TBF (mo)	*P**
BMI at age 25			
Non-obese	57	34.4	0.83
Overweight	30	31.7	
Obese	6	33.7	
BMI at age 40			
Nonobese	36	34.9	0.86
Overweight	38	33.0	
Obese	20	31.5	
BMI at diagnosis			
Nonobese	23	36.9	0.48
Overweight	44	34.6	
Obese	29	26.6	
Weight change age 25 to diagnosis (kg/y)			
Loss/no change/gain, <0.5	64	39.0	0.005 †
Gain, 0.5-1.5	24	23.7	
Gain, >1.5	7	16.7	

Abbreviation: TBF, time to biochemical failure.
*Mann-Whitney *U* test.
†Kruskal-Wallis test.

limited and results have been unclear (9). The association between obesity and prostate cancer progression/mortality is supported by several lines of independent evidence. In a large cohort of Swedish construction workers, high BMI was associated with prostate cancer mortality (10). The Cancer Prevention Study II also reported an increased risk of prostate cancer mortality among severely obese men (11). We and others have suggested that among men with clinically localized disease, the risk of being diagnosed with more aggressive tumors is greater in men with higher BMI (12, 13). These results suggest that body mass could be a better predictor of aggressiveness and more likely implicated in prostate cancer progression than in incidence.

Two recent retrospective studies support our hypothesis that obesity plays a role in biochemical failure among patients treated with radical prostatectomy. Amling et al. (5) found that among 3,162 men treated with prostatectomy, BMI was associated with adverse pathologic variables (Gleason score, PSA, and stage) but did not have an independent effect on biochemical failure. Freedland et al. (6) in a similar group of 1,106 prostatectomy patients with a median follow-up of 33 months reported that BMI ($\geq$35 kg/m^2) and high PSA and Gleason score were independent predictors of biochemical failure. In our study, there were a total of 23 patients with BMI $\geq$ 35 kg/m^2 at diagnosis, eight at age 40, and only one at 25. The failure rates were 8 of 23 (34%), 8 of 40 (20%), and zero of one (0%), respectively. Although the overall rate of failure was elevated in this group, the numbers were too small to make any conclusions.

Among the 526 patients in our study population the overall observed biochemical failure was 17% with an average follow-up of 54 months. Although the number of African American patients was limited, they had a slightly higher failure rate (20%) than Whites (17%). Our results confirm the recent report that obesity as measured by BMI at time of diagnosis is an independent predictor of biochemical failure (6). A major health care concern is the effect of obesity over time. To address this, we analyzed the effect of obesity at different ages before diagnosis (e.g., age 25 and 40) and weight gain over time. Our data suggest that being obese at age 40 and at diagnosis are strong predictors and may provide further insight into the natural history of prostate cancer. Relevant are our findings that obese men and especially those who had the largest weight gained over time had a shorter mean time to biochemical failure. These findings strengthen the previously reported association between obesity and advance disease supporting the view that the development of aggressive forms of prostate cancer, in addition to prostate cancer in general, may be influenced by environmental effects that occur early in life.

We believe ours is the first study to investigate the association between BMI at different ages and adult weight gain rate on biochemical failure among a uniform group of prostatectomy patients followed prospectively.

Weight gain is the result of an energy imbalance when expenditure is less than intake. It has been postulated that hormones, diet, and alcohol provide an estrogen-like environment, which may result in delaying cancer development, thereby, lowering risk or postponing prostate cancer initiation. In adulthood, weight gain probably reflects increasing fat body mass as lean mass in adulthood tends to be stable, slowly

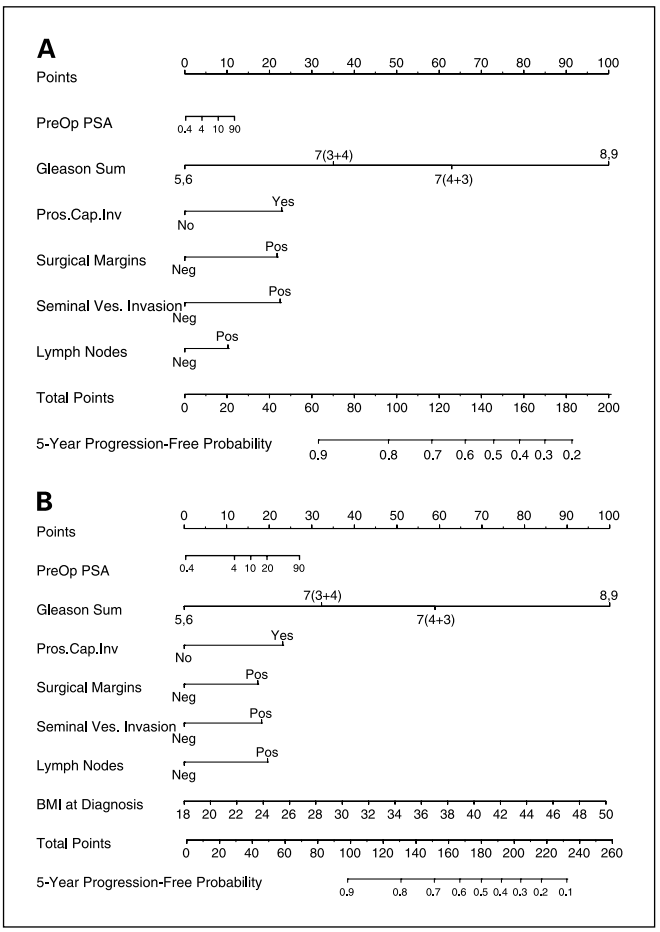

Fig. 2. *A*, nomogram without BMI. *B*, nomogram with BMI.

decreasing with aging (14). In animal studies, restriction of energy intake inhibits prostate carcinogenesis (4). Energy imbalance is possibly important, but hormonal changes associated with obesity could obscure these associations (15). Obesity has been associated with lower testosterone levels (16) and more advanced prostate cancer (17, 18). Additionally, obesity results in higher insulin and insulin-like growth factor-I levels (19, 20), both of which are mitogenic and antiapoptotic and have been associated with advanced prostate cancer (21, 22). A correlation between total serum insulin-like growth factor-I levels and testosterone (23) and diet has been reported (24). Recently, it has been suggested that prostate cancer could be another aspect of the insulin resistance syndrome (15). In this model, environmental factors, such as body weight, physical activity, or diet, could modify insulin resistance affecting the final phenotype. Epidemiologic evidence suggests that insulin resistance is associated with increased prostate cancer risk (25, 26) and high Gleason score (22, 27). However, there are no data on the role of these hormones in prostate cancer progression. The interrelationships between these hormones and obesity are extremely complex and well-designed studies will be needed to clarify the underlying mechanisms between obesity and prostate cancer progression.

Our study included a clinically homogeneous group of patients from a single institution who were followed for at least 6 months after surgery. We have complete follow-up information for 98% of the patients. There are inherent limitations in our study. This study is hospital-based and the patient population of the M.D. Anderson Cancer Center is subject to the vagaries of referral patterns. However, our cases are similar to other reported hospital series with respect to stage, Gleason score, PSA levels, and age (28). BMI is the most widely used anthropometric measurement; however, its use is limited as it does not truly distinguish between adiposity and lean body mass. We used self-reported height and weight to calculate BMI at different ages. It has been shown that self-reported and investigator measured height and weight are well correlated (29).

In summary, our findings validate the importance of energy balance in prostate cancer progression and suggest a link to the biological basis of prostate cancer progression that can be therapeutically exploited. We also developed a nomogram adding BMI to the clinicopathologic characteristics that has an improved ability to predict biochemical progression. This nomogram will need to be validated in a larger multi-institutional series of patients followed for a longer period of time.

Future directions will emphasize evaluating the relationship of obesity with dietary factors, genetic modifiers of steroid androgen metabolism, insulin, and a detailed investigation of the insulin growth factor pathway to explore the underlying mechanisms of action in prostate carcinogenesis. Understanding the mechanisms by which weight gain contributes to prostate cancer progression will lead to rationally designed neoadjuvant and adjuvant therapies.

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