Inverse Correlation Between Body Mass Index and Clinical Outcomes in Men With Advanced Castration–Recurrent Prostate Cancer

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Supported in part by grants from the Department of Defense DAMD 17-03-1-0112 and the National Cancer Institute (CA 36601).

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Received January 23, 2007; revision received March 22, 2007; accepted March 28, 2007.

BACKGROUND. Obesity has a variety of adverse health outcomes, but to the authors' knowledge, the effect of obesity on outcome in patients with advanced prostate cancer is not known. For this reason, the correlation between an elevated body mass index (BMI) and clinical outcomes in patients with metastatic, castration-recurrent prostate cancer (CRPC) was evaluated.

METHODS. A total of 1226 men with CRPC who were enrolled in 9 prospective clinical trials conducted by the Cancer and Leukemia Group B (CALGB) for the treatment of metastatic disease were considered. Eligible patients had progressive prostate cancer during androgen deprivation therapy (with documented castrate levels of testosterone); an Eastern Cooperative Oncology Group performance status of 0 to 2; and adequate hematologic, renal, and hepatic function. Patients were classified based on BMI as normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and mildly to severely obese ($\geq$30 kg/m^2).

RESULTS. Approximately 24% of the patients had a normal BMI, 43% were overweight, and 33% were mildly to severely obese. On multivariable analysis, BMI was found to be a statistically significant predictor of overall survival and prostate cancer–specific mortality. Compared with men with normal BMIs, the hazard ratios for death for overweight men and mildly to severely obese men were 0.80 (95% confidence interval [95% CI], 0.68–0.93; $P = .001$) and 0.80 (95% CI, 0.68–0.94; $P = .010$), respectively.

CONCLUSIONS. In patients with metastatic CRPC, obesity (as defined by an elevated BMI) appears to have a protective effect against overall mortality and prostate cancer–specific mortality. Alternatively, a higher BMI may reflect different cancer biology (ie, the lack of cachexia-producing substances). Further studies to gain a more comprehensive understanding of the mechanisms behind these clinical observations are needed. *Cancer* 2007;110:1478–84. © *2007 American Cancer Society.*

KEYWORDS: obesity, castration-recurrent prostate cancer, race, clinical outcomes.

It is estimated that approximately two-thirds of the U.S. population are either overweight or obese.[1] Obesity has been shown to increase the risk of heart disease, diabetes, and cancer.[2–4] The association between obesity and the risk of certain malignancies, such as colon cancer, postmenopausal breast cancer, and renal cell carcinoma, is reasonably well established. There has been some evidence linking obesity with prostate cancer risk, although this remains an issue of considerable debate.

However, there is burgeoning evidence that obese prostate cancer patients have less favorable outcomes compared with their normal-weight counterparts.[2–16] A substantial body of research has emerged in recent years with regard to obesity and its effect on various outcomes

DOI 10.1002/cncr.22932
Published online 30 July 2007 in Wiley InterScience (www.interscience.wiley.com).

such as pathologic findings at the time of radical prostatectomy,[5] biochemical (prostate-specific antigen [PSA]) disease progression,[6–16] and clinical disease progression.[16]

To our knowledge, the majority of the literature published to date consists of studies of men with hormone-sensitive disease. However, little is known regarding the role of obesity in men with progressive prostate cancer despite androgen deprivation therapy, herein referred to as castration-recurrent prostate cancer (CRPC). Reports by Amling et al.[11] and Freedland et al.[13] linking obesity and adverse outcomes in patients with localized (hormone-sensitive) prostate cancer were the basis for the current evaluation of the correlation between obesity or body mass index (BMI) with clinical outcomes in 1296 men with CRPC who were enrolled on clinical trials conducted by the Cancer and Leukemia Group B (CALGB). We asked the question as to whether an elevated BMI is predictive of worse clinical outcomes in men with CRPC. A preliminary analysis of the impact of BMI on overall survival was published previously elsewhere.[17]

MATERIALS AND METHODS

Study Population

Combined data from 1296 men with CRPC who were treated on 9 CALGB multi-institutional clinical trials between 1991 and 2004 were evaluated. Eligible patients were men with prostate cancer that had progressed during castrate levels of testosterone. Patients who had received prior treatment with chemotherapy, immunotherapy, or other nonhormonal therapy were excluded from these trials. In addition, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate hematologic, renal, and hepatic function were required. Additional details regarding these trials have been published elsewhere.[18,19] Each participant signed an Institutional Review Board–approved, informed consent document in accordance with federal and institutional guidelines.

Statistical Considerations

The primary endpoint considered was overall survival (OS), which was defined as the time from the date of randomization or study entry to the date of death. In addition, the effect of BMI on other endpoints was explored, including prostate cancer–specific–free survival (PCSFS), progression–free survival (PFS), a $\geq$50% decline in PSA as a consequence of protocol treatment, and objective (bidimensionally measurable) response proportion. PCSFS was defined as the time from the date of randomization or study entry to the date of patient death due to prostate cancer. The principal investigators of each study determined the cause of death for each patient based on the case report forms submitted by the local treating physician. PFS was defined as the time from the date of randomization or study entry to the date of first disease progression (PSA, clinical, or bone) or death, whichever occurred first. A 50% decline in post–therapy PSA was defined as a $\geq$50% decline in PSA from baseline confirmed by a second determination at least 2 weeks apart. Although PSA Consensus Criteria were not developed at the time several of these trials were conducted, these standard criteria were used for retrospective analysis of the data.[20]

BMI at study entry was defined as the ratio of weight (in kg) divided by height squared (in meters). The National Institutes of Health (NIH) definition for classifying patients on the basis of BMI was utilized, which uses the following categories: underweight (BMI $<$18.5 kg/m^2), normal (BMI of 18.5–24.9 kg/m^2), overweight (BMI of 25–29.9 kg/m^2), mildly obese (BMI of 30–34.9 kg/m^2), and moderately to severely obese (BMI $\geq$35 kg/m^2). There were 11 men who were underweight (BMI $<$18.5 kg/m^2) and these patients were excluded from the analysis. Furthermore, due to a paucity of events (deaths) in the moderately to severely obese (BMI $\geq$35 kg/m^2) group, these men were categorized in the mildly obese group (BMI $\geq$30 kg/m^2). In addition, 59 patients who had either missing height or weight data were excluded from the analysis, which lead to a final sample size of 1226 men.

The Kaplan–Meier product–limit[21] method was used to estimate the OS, PCSFS, and PFS distributions by the BMI. Because of an observed trend for an increased BMI over time, the proportional hazards model was used to assess the prognostic significance of BMI in predicting clinical outcomes and was used for stratifying by protocol, which basically is the year of treatment. The proportional hazards assumption was assessed using a global test based on the Schoenfeld residuals.[22] In addition, the logistic regression model was used to assess the prognostic significance of BMI in predicting the probability of experiencing an objective (bidimensional mass) response and the probability of a $\geq$50% decline in post–therapy PSA.

On the multivariable models, men who had a normal BMI index were considered as the reference group. Known and established prognostic variables,[23,24] including age, race, ECOG performance status, Gleason score, hemoglobin, testosterone, PSA, alkaline phosphatase, lactate dehydrogenase (LDH), the presence of visceral disease, prior treatment with radiotherapy, and years since diagnosis, were included in the multivariate models. Age, hemoglobin, and testosterone were modeled as continuous variables whereas race, ECOG performance status, Gleason score, the presence of

TABLE 1
Baseline Clinical and Laboratory Variables by BMI

	BMI of 18.5–24.9 kg/m^2	BMI of 25–29.9 kg/m^2	BMI ≥30 kg/m^2	All Patients	
	N = 300, %	N = 521, %	N = 405, %	N = 1226, %	*P*
Age (interquartile range), y*	73 (67–78)	72 (66–76)	69 (63–75)	71 (65–76)	<.001
Race					
Caucasian	83	84	82	83	
African-American	13	14	15	14	
Other	4	2	3	3	.472
Years since diagnosis (interquartile range)*	3.6 (1.8–6.5)	4.0 (2.1–6.9)	3.7 (1.9–6.0)	3.7 (2.0–6.4)	.221
Gleason score†					
2–4	8	7	9	8	
5–7	46	47	47	47	
8–10	46	46	44	45	.717
ECOG performance status					
0	32	47	49	44	
1	51	44	44	46	
2	17	9	7	10	<.001
Disease measurability					
Measurable	36	38	35	37	
Evaluable	64	62	65	64	.706
Metastases‡					
Any	99	98	97	98	.102
Visceral	17	14	11	14	.132
Bone	91	89	88	89	.359
Lymph node	36	34	33	34	.640
Hemoglobin (interquartile range), g/dL	11.8 (10.7–13.0)	12.5 (11.5–13.5)	12.7 (11.6–13.7)	12.4 (11.3–13.4)	<.001
PSA (interquartile range), ng/mL	157 (52–417)	93 (32–271)	114 (39–290)	111 (39–312)	<.001
Alkaline phosphatase (interquartile range), U/L	168 (102–381)	150 (94–309)	138 (95–275)	150 (96–309)	.055
LDH (interquartile range), U/L	239 (174–444)	212 (173–402)	212 (174–391)	216 (173–416)	.206
Creatinine (interquartile range), mg/dL	1.0 (0.9–1.2)	1.1 (0.9–1.2)	1.0 (0.9–1.2)	1.0 (0.9–1.2)	.033
Testosterone (interquartile range), ng/mL	17 (10–21)	16 (9–23)	20 (10–25)	18 (10–23)	.151
Prior radiotherapy	59	53	49	53	.040
Prostatectomy	25	25	26	25	.862
LHRH agonists‡	59	63	70	65	.012
Surgical castration‡	52	46	36	44	<.001

BMI indicates body mass index; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LDH, lactate dehydrogenase; LHRH, luteinizing hormone-releasing hormone.
* Median (interquartile range); *P* was derived from the Wilcoxon signed-rank test.
† Collected as a categoric factor.
‡ Patients may have had >1 response.

visceral disease, and prior treatment with radiotherapy were modeled as categoric variables. LDH, years since diagnosis, alkaline phosphatase, and PSA were modeled using the restricted cubic spline function because they had skewed distribution. S–plus statistical software was used for the data analyses and all statistical tests were 2–sided.

RESULTS

Baseline Characteristics

The baseline clinical and laboratory characteristics of the 1226 patients are summarized in Table 1. Approximately 24% (300 patients) of the patients had a normal BMI (18.5–24.9 kg/m^2), 43% (521 patients) were in the overweight category (25–29.9 kg/m^2), and 33% (405 patients) were in the mildly to severely obese category (≥30 kg/m^2). There were statistically significant differences noted with regard to age, ECOG performance status, hemoglobin levels, and PSA levels across BMI categories. However, there were no statistically significant differences noted in BMI by racial groups.

Men who were moderately or severely obese had a better ECOG performance status, higher levels of hemoglobin, and lower PSA levels than men with a normal BMI. Furthermore, a higher proportion of men in the obese group received medical castration compared with men in the normal BMI and overweight groups. This finding was statistically significant.

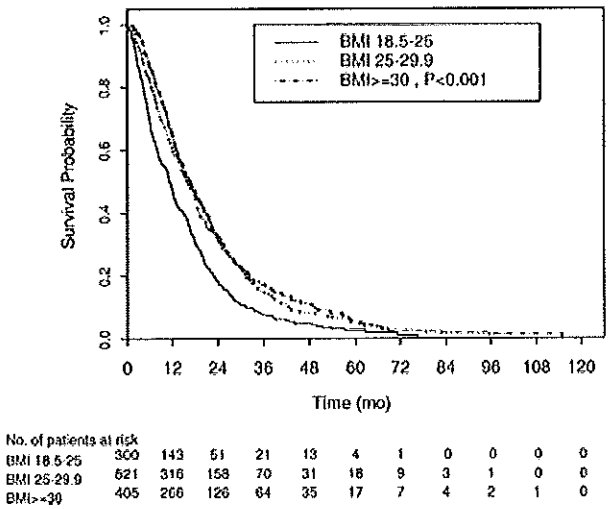

FIGURE 1. Kaplan–Meier survival curves by body mass index (BMI).

Overall Survival

Of the 1226 men, 94% had died by the time of the current analysis, and the median follow-up among surviving patients was 33.8 months (95% confidence interval [95% CI], 24.4–41.4 months). The survival times were found to be statistically correlated with BMI. The median survival times were 11.5 months (95% CI, 9.3–12.7 months) for men with normal a BMI, 16.1 months (95% CI, 14.2–17.8 months) for overweight men, and 16.9 months (95% CI, 15.0–18.5 months) for mildly to severely obese men ($P < .001$) (Fig. 1).

The results of the multivariable analysis for OS are presented in Table 2. BMI was found to be a statistically significant predictor of survival time. Compared with men with a normal BMI, the adjusted hazard ratios (HRs) for death for overweight patients was 0.80 (95% CI, 0.68–0.93; $P = .001$) and was 0.80 for mildly to severely obese patients (95% CI, 0.68–0.94; $P = .010$).

Prostate Cancer–Specific–Free Survival

Of 1152 patients who had died at the time of last follow-up, 84% were determined to have died of prostate cancer. The median times to prostate cancer death were 12.7 months (95% CI, 11.3–15.8 months) for men with normal BMIs, 17.6 months (95% CI, 15.7–18.7 months) for overweight men, and 18.9 months (95% CI, 16.7–20.9 months) for mildly to severely obese men ($P < .001$). Compared with men with a normal BMI, the HR for prostate cancer death was 0.82 (95% CI, 0.70–0.97; $P = .02$) for overweight patients and was 0.81 (95% CI, 0.68–0.97; $P = .02$) for mildly to severely obese men (Table 3).

TABLE 2
Multivariable Proportional Hazards Model With BMI as a Predictor of Overall Survival Stratified on Protocol

Factor	HR (95% CI)	P
BMI, kg/m^2		
25–29.9 vs <25	0.80 (0.68–0.93)	.001
≥30 vs <25	0.80 (0.68–0.94)	.010
ECOG performance status		
1 vs 0	1.36 (1.19–1.55)	<.001
2 vs 0	1.88 (1.51–2.33)	<.001
Presence of visceral disease		
Yes vs no	1.34 (1.12–1.60)	.001
Prior radiotherapy		
Yes vs no	1.25 (1.09–1.43)	<.001
Gleason score		
8–10 vs 2–7	1.23 (1.09–1.39)	.001
Age*	1.07 (0.99–1.16)	.08
Testosterone*	1.01 (1.00–1.02)	.06
Hemoglobin	0.89 (0.86–0.93)	<.001
Race		
African American vs white and others	0.82 (0.69–0.98)	.05
Alkaline phosphatase†	–	<.001
Years since diagnosis†	–	<.001
PSA†	–	<.001
LDH†	–	<.001

BMI indicates body mass index; HR, hazard ratio; 95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.
* Hazards ratio based on 10-unit change in the variable.
† Modeled as a restricted cubic spline.

Progression–Free and PSA Progression–Free Survival

The median times to first disease progression (clinical disease progression, bone progression, PSA progression, or death) were 2.5 months (95% CI, 2.2–2.8 months) for men with a normal BMI, 2.6 months (95% CI, 2.2–3.0 months) for overweight men, and 2.7 months (95% CI, 2.5–3.1 months) for mildly to severely obese men ($P = .022$). On multivariate analysis, BMI was not found to be a statistically significant predictor of PFS. Compared with men with a normal BMI, the HR for disease progression in overweight patients was 0.90 (95% CI, 0.78–1.05; $P = .18$) and 0.89 (95% CI, 0.76–1.05; $P = .16$) for mildly to severely obese men (Table 4).

The median times to biochemical (PSA) progression were 3.9 months (95% CI, 3.4–4.6 months) for men with a normal BMI, 4.3 months (95% CI, 3.7–5.0 months) for overweight men, and 4.7 months (95% CI, 3.7–5.9 months) for mildly to severely obese men ($P = .03$). The adjusted HRs for biochemical progression were 0.98 (95% CI, 0.84–1.14; $P = .81$) and 0.92 (95% CI, 0.78–1.07; $P = .27$) for mildly to severely obese men, respectively (data not presented).

TABLE 3
Multivariable Proportional Hazards Model With BMI as a Predictor of Prostate Cancer-Specific-Free Survival Stratified on Protocol

Factor	HR (95% CI)	P
BMI, kg/m^2		
25–29.9 vs <25	0.82 (0.70–0.97)	.02
≥30 vs <25	0.81 (0.68–0.97)	.02
ECOG performance status		
1 vs 0	1.41 (1.22–1.62)	<.001
2 vs 0	1.81 (1.42–2.29)	<.001
Presence of visceral disease		
Yes vs no	1.47 (1.22–1.77)	<.001
Prior radiotherapy		
Yes vs no	1.26 (1.09–1.46)	.002
Gleason score		
8–10 vs 2–7	1.25 (1.09–1.43)	.001
Age*	1.03 (0.94–1.12)	.51
Testosterone*	1.01 (1.00–1.03)	.15
Hemoglobin	0.88 (0.84–0.93)	<.001
Race		
African American vs white and others	0.85 (0.70–1.02)	.08
Alkaline phosphatase†	–	<.001
Years since diagnosis†	–	<.001
PSA†	–	<.001
LDH†	–	<.001

BMI indicates body mass index; HR, hazard ratio; 95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.
* Hazard ratio based on 10-unit change in the variable.
† Modeled as a restricted cubic spline.

TABLE 4
Multivariable Proportional Hazards Model With BMI as a Predictor of Progression-Free Survival Stratified on Protocol

Factor	HR (95% CI)	P
BMI, kg/m^2		
25–29.9 vs <25	0.90 (0.78–1.05)	.18
≥30 vs <25	0.89 (0.76–1.05)	.16
ECOG performance status		
1 vs 0	1.22 (1.08–1.39)	.002
2 vs 0	1.59 (1.28–1.97)	<.001
Presence of visceral disease		
Yes vs no	1.18 (0.99–1.40)	.06
Prior radiotherapy		
Yes vs no	1.12 (0.98–1.28)	.09
Race		
African American vs white and others	1.12 (0.94–1.33)	.21
Gleason score		
8–10 vs 2–7	1.07 (0.95–1.21)	.28
Testosterone*	1.00 (0.99–1.01)	.94
Hemoglobin	0.99 (0.95–1.03)	.61
Age*	0.95 (0.88–1.02)	.16
Alkaline phosphatase†	–	<.001
Years since diagnosis†	–	.112
PSA†	–	.09
LDH†	–	.001

BMI indicates body mass index; HR, hazard ratio; 95% CI, 95% confidence interval; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen; LDH, lactate dehydrogenase.
* Hazard ratio based on 10-unit change in the variable.
† Modeled as a restricted cubic spline.

Objective Response and 50% Decline in Post–therapy Changes in PSA

The association between BMI and objective response was also explored. Men with a normal BMI were found to have the lowest objective response rate compared with men with a higher BMI. Men who were overweight were 1.94 more likely to respond (95% CI, 0.94–4.00; $P = .07$) than men who had a normal BMI. Furthermore, the unadjusted odds ratio (OR) for response was 2.1 (95% CI, 1.0–4.4; $P = .05$) for men who were mildly to severely obese compared with men with a normal BMI. On multivariable logistic regression analysis adjusted for race and ECOG performance status, the ORs for objective response were 1.85 (95% CI, 0.89–3.84; $P = .09$) for men who were mildly to severely obese and 2.00 (95% CI, 0.94–4.27; $P = .07$) for men who were overweight compared with men with normal BMIs.

However, there was no association noted between BMI and post–therapy changes in PSA. Men with a normal BMI (33%) had similar proportions of ≥50% decline in PSA compared with overweight men (35%) or mildly to severely obese men (34%) ($P = .74$).

DISCUSSION

The results of this retrospective analysis demonstrate a protective effect of elevated BMI on clinical outcomes in men with metastatic CRPC. On multivariable models, men with a BMI of 25 to 29.9 kg/m^2 and a BMI of ≥30 kg/m^2 were found to have longer survival times and time to prostate cancer death than men with normal BMIs. Furthermore, although not statistically significant, there was a trend toward a lower HR of disease progression and higher objective response rates among overweight or mildly to severely obese men compared with normal men.

These results stand in contrast to data reported for men with localized, hormone-sensitive disease, in whom obesity is an adverse risk factor for a variety of clinical outcomes. However, the correlation between obesity and outcomes for patients with prostate cancer is both complex and not well understood. Part of the difficulty in elucidating this correlation is that any meaningful analysis involving obesity must adjust for potential confounding variables such as race, age, socioeconomic status, and comorbidities. Large prospective studies have demonstrated an association between obesity and prostate cancer mortality.[25,26] Using data from the Cancer Prevention Study I and II,

Rodriguez et al. observed that obese men were at a higher risk of dying of prostate cancer.[25] Furthermore, in an analysis of 404,576 men enrolled in the Cancer Prevention Study II, Calle et al. indicated a statistically significant linear trend in prostate cancer mortality with an elevated BMI.[26]

Several studies have shown that obesity increases the risk of prostate cancer recurrence and disease progression in men with localized disease who were treated with radical prostatectomy.[6–13,16] In a study of 3162 men who underwent radical prostatectomy, Amling et al. reported that an elevated BMI was associated with a greater frequency of adverse pathologic outcomes.[11] Obese patients, defined as having a BMI $\geq$30 kg/m^2, had higher–grade disease and more frequently positive surgical margins. Although the univariate HR for a BMI $\geq$30 kg/m^2 was found to be statistically significant (HR of 1.20; 95% CI, 1.02–1.42 [$P = .028$]) on multivariable analysis, BMI was not found to be a statistically significant predictor of biochemical failure–free survival. Similarly, Freedland et al. assessed the correlation between obesity and time to biochemical disease progression in 1106 men who were treated with radical prostatectomy using the SEARCH database.[13] On multivariate analysis, the HR for biochemical failure was 2.09 (95% CI, 1.30–3.37; $P = .002$) for patients with a BMI indicating moderate to extreme obesity compared with men who had a normal BMI. In an analysis of 2796 men treated at a single institution (Johns Hopkins), Freedland et al. confirmed this observation.[9] In a recent study that used data regarding 2131 men who underwent radical prostatectomy from the CaPSURE database, Bassett et al. demonstrated that very obese men (BMI of $\geq$35 kg/m^2) had a higher risk of disease recurrence than men with a lower BMI.[12] Unlike the studies by Amling et al. and Freedland et al., the current study controlled for significant comorbidities such as diabetes on the multivariate model, and confirmed the correlation between BMI and biochemical failure in men treated with radical prostatectomy. Of the above studies, the report by Strom et al. was among the few that investigated BMI at more than 1 timepoint (BMI at age at diagnosis and BMI at age 40 years) and observed a statistically significant correlation between obesity and biochemical disease recurrence of prostate cancer in men who underwent radical prostatectomy.[7] Moreover, the authors observed a similar correlation between obesity and biochemical failure and clinical disease progression in 939 men treated with external beam radiotherapy.[15]

The protective effect of an elevated BMI that was observed in the current analysis is in contrast to previously published findings in men with earlier stage disease. We hypothesize that in this population of men with advanced disease, a lower BMI may reflect cancer cachexia and may serve as surrogate of more aggressive disease, leading to more rapid disease progression or less effective treatment. Indeed, in the patient population evaluated in the current study, a normal BMI was found to be associated with a statistically significantly lower ECOG performance status, lower levels of hemoglobin, and higher PSA levels than those found in men with an elevated BMI. Alternatively, obese men may have a higher protein and calorie reserve, allowing them to withstand the cachexia–producing effects of advancing CRPC. It is unclear whether there is a mechanistic biologic link between obesity and short–term protection from prostate cancer–induced death. Androgen deprivation therapy apparently induces weight gain, obesity, and the metabolic syndrome.[27] All men in the current study had undergone androgen deprivation therapy and were maintained on such. Several studies have demonstrated that caloric intake and energy imbalance play an important role in this correlation.[28]

Some authors have suggested that certain hormones associated with obesity, such as leptin and insulin–like growth factor–1 (IGF–I), stimulate the growth of prostate cancer cells. Obesity is associated with higher IGF–1 levels and leptin.[29–34] However, the correlation may be dynamic. Recently, adiponectin, a major adipose cytokine that decreases in circulation in obesity and ameliorates obesity, was identified as an inhibitor of prostate cancer cell growth.[35] Furthermore, a fragment of adiponectin, f–adiponectin, suppresses leptin–stimulated and/or IGF–1–stimulated, androgen–independent prostate cancer cell line (DU145) growth, as well as dihydrotestosterone–stimulated, androgen–dependent prostate cancer cell line (LNCaP-FGC) growth. In addition, f–adiponectin enhances doxorubicin's inhibition of prostate cancer cell growth.

The strengths of the current analysis were that the information regarding treatment and the eligibility criteria were prospectively defined and collected. Unlike the majority of studies reported in the literature, weight and height were measured in all men before the initiation of chemotherapy and were not based on self–report. The main limitation of the current study is that BMI was not measured before the diagnosis of prostate cancer. However, our clinical experience in this patient population, who are older and have advanced disease, is that BMI rarely decreases dramatically until the patient's disease is refractory to chemotherapy and cancer cachexia has set in.

The findings from the current study suggest that obesity has an impact on clinical outcomes associated with CRPC, in contrast to earlier stages of prostate cancer. Further studies of the mechanisms underlying this

correlation as well as a prospective validation of these results are warranted.

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among U.S. adults, 1999–2000. *J Am Med Dir Assoc.* 2002;288:1723–1727.
2. Criqui MH, Mebane I, Wallace RB, et al. Multivariate correlates of adult blood pressures in nine North American populations: The Lipid Research Clinics Prevalence Study. *Prev Med.* 1982;11:391–402.
3. Hubert HB, Freinleib M, McNamra PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26–year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;67:968–977.
4. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes and obesity related health risk factors. *JAMA* 2003;289:76–79.
5. Presti JC, Jr, Lee U, Brooks JD, et al. Lower body mass index is associated with a higher prostate cancer detection rate and less favorable pathological features in a biopsy population. *J Urol.* 2004;171:2199–2202.
6. Amling CL, Kane CJ, Riffenburgh RH, et al. Relationship between obesity and race in predicting adverse pathologic variables in patients undergoing radical prostatectomy. *Urology.* 2001;58:723–728.
7. Strom SS, Wang X, Pettaway CA, et al. Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy. *Clin Cancer Res.* 2005;11: 6889–6894.
8. Kane CJ, Bassett WW, Sadetsky N, et al. Obesity and prostate cancer clinical risk factors at presentation: data from CaPSURE. *J Urol.* 2005;173:732–736.
9. Freedland SJ, Grubb KA, Yiu SK, et al. Obesity and risk of biochemical progression following radical prostatectomy at a tertiary care referral center. *J Urol.* 2005;174:919–922.
10. Freedland SJ, Terris MK, Presti JC Jr, et al. Obesity and biochemical outcome following radical prostatectomy for organ confined disease with negative surgical margins. *J Urol.* 2004;172:520–524.
11. Amling CL, Riffenburgh RH, Sun L, et al. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. *J Clin Oncol.* 2004;22:439–445.
12. Bassett WW, Cooperberg MR, Sadetsky N, et al. Impact of obesity on prostate cancer recurrence after radical prostatectomy: data from CaPSURE. *Urology.* 2005;66:1060–1065.
13. Freedland SJ, Aronson WJ, Kane CJ, et al. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the shared equal access regional cancer hospital database study group. *J Clin Oncol.* 2004;22:446–453.
14. Freedland SJ, Platz EA, Presti JC, et al. Obesity, serum prostate specific antigen and prostate size: implications for prostate cancer detection. *J Urol.* 2006;175:500–504.
15. Strom SS, Kamat AM, Gruschkus SK, et al. Influence of obesity on biochemical and clinical failure after external–beam radiotherapy for localized prostate cancer. *Cancer.* 2006; 107:631–639.
16. Merrick GS, Butler WM, Wallner KE, et al. Influence of body mass index on biochemical outcome after permanent prostate brachytherapy. *Urology.* 2005;65:95–100.
17. Halabi S, Small EJ, Vogelzang NJ. An elevated body mass index predicts for longer overall survival duration in men with metastatic hormone refractory prostate cancer (HRPC). *J Clin Oncol.* 2005;23:2434–2435.
18. Farkas A, Marcella S, Rhoads GG. Ethnic and racial differences in prostate cancer incidence and mortality. *Ethn Dis.* 2000;10:69–75.
19. Mettlin CJ, Murphy GP. Why is the prostate cancer death rate declining in the United States? *Cancer* 1998;82:249–251.
20. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen independent prostate cancer: recommendations from the PSA working group. *J Clin Oncol.* 1999;17:3461–3467.
21. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457–481.
22. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika.* 1982;69:239.
23. Halabi S, Small EJ, Kantoff PW, et al. Prognostic model for predicting survival in men with hormone–refractory metastatic prostate cancer. *J Clin Oncol.* 2003;21:1232–1237.
24. Smaletz O, Scher HI, Small EJ, et al. Nomogram for overall survival of patients with progressive metastatic prostate cancer after castration. *J Clin Oncol.* 2002;20:3972–3982.
25. Rodriguez C, Patel AV, Calle EE, et al. Body mass index, height, and prostate cancer mortality in two large cohorts of adult men in the United States. *Cancer Epidemiol Biomarkers Prev.* 2001;10:345–353.
26. Calle EE, Rodrigues C, Walker–Thurmond K, et al. Overweight, obesity and mortality from cancer in a prospectively studies cohort of U.S. adults. *N Engl J Med.* 2003;348:1625–1638.
27. Flanagan JR, Carney–Doebbeling C, Jones L, et al. Metabolic syndrome predicts for shorter response to hormonal therapy in prostate cancer. 2006 ASCO Annual Meeting Proceedings Part I. *J Clin Oncol.* 2006;24(18Suppl).
28. Platz EA, Leitzmann MF, Michaud DS, et al. Interrelation of energy intake, body size, and physical activity with prostate cancer in a large prospective cohort study. *Cancer Res.* 2003; 63:8542–8548.
29. Chan JM, Stamfer MJ, Giovannucci E, et al. Plasma insulin–like growth factor 1 in relation to prostate cancer risk: a prospective study. *Science.* 1998;279:563–566.
30. Pummer K, Stettner H, Trummer H, et al. Body mass is an independent predictor for organ confined prostate cancer. *J Urol.* 2000;163:183(Suppl Abstract 809).
31. Schatzl G, Madersbacher S, Thurridl T, et al. High–grade prostate cancer is associated with low serum testosterone levels. *Prostate.* 2001;47:52–57.
32. Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol.* 2003;169:1670–1675.
33. Frystyk J, Vestbo E, Skjaerback C, et al. Free insulin–like growth factors in human obesity. *Metabolism.* 1995;44:37–44.
34. Freedland SJ, Aronson WJ. Obesity and prostate cancer. *Urology.* 2005;65:433–439.
35. Bub JD, Miyazaki T, Iwamoto Y. Adiponectin as a growth inhibitor in prostate cancer cells. *Biochem Biophys Res Commun.* 2006;340:1158–1166.