Association of Body Mass Index With Prostate Cancer Biochemical Failure

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Purpose: The association between obesity and biochemical failure measured by prostate specific antigen after prostate cancer treatment is controversial. We determined whether there is an association between body mass index and biochemical failure in men treated for low and intermediate risk prostate cancer with various treatment modalities.

Materials and Methods: We performed a cohort study in 2,687 patients who underwent treatment for low and intermediate risk prostate adenocarcinoma as described by National Comprehensive Cancer Network guidelines at Cleveland Clinic between January 1996 and December 2005. Univariate and multivariate analyses were done to determine the effect of multiple patient characteristics on biochemical failure.

Results: There were 319 biochemical failures (11.9%). Body mass index as a continuous variable was significantly associated with biochemical failure on univariate analysis (HR 1.030, $p = 0.02$). There was a significant association with biochemical failure when comparing normal vs overweight and normal vs obese men but not overweight vs obese men. On multivariate analysis body mass index as a continuous or a categorical variable was not significantly associated with biochemical failure. Multivariate analysis revealed certain variables significantly associated with biochemical failure, including black race, greater initial prostate specific antigen, Gleason score 7, treatment type and more frequent prostate specific antigen screening.

Conclusions: We found a significant association between body mass index and biochemical failure on univariate analysis that did not hold true on multivariate analysis. Black race was associated with biochemical failure on multivariate analysis. The reason for this is unclear. Future studies should further characterize the relationship between race and biochemical failure.

Key Words: prostate, adenocarcinoma, African continental ancestry group, body mass index, prostate-specific antigen

Abbreviations and Acronyms

AD = androgen deprivation
bF = biochemical failure
bFFS = bF-free survival
BMI = body mass index
EBRT = external beam radiotherapy
IGF-1 = insulin-like growth factor 1
IMRT = intensity modulated radiation therapy
PB = prostate brachytherapy
PSA = prostate specific antigen
RP = radical prostatectomy

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In the last 20 years obesity in the United States has increased to dramatic levels. Between 1999 and 2004 obesity in American men increased from 27.5% to 31.1%.[1] Although the causality of prostate cancer due to increased obesity is debated, obese men are more likely to have more advanced disease.[2]

The metabolic effects of obesity may have a role in prostate cancer risk and treatment outcomes. Obese individuals are more likely to have increased IGF-1 and estrogen, and decreased sex hormone binding globulin.[3] In a hyperinsulinemic state of obesity growth hormone, a key IGF-1 regulator, is decreased. Increased IGF-1 is thought

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to have a role in prostate cancer progression.[4] A meta-analysis showed that increased IGF-1 is associated with an increased prostate cancer risk (OR 1.21, p <0.003).[5] A lower testosterone-to-sex hormone binding globulin ratio may be associated with greater prostate cancer risk in older men.[6] Obese men are more likely to have lower testosterone, which is associated with higher prostate cancer stage.[7] These biological associations with obesity may be the cause of increased mortality due to prostate cancer.[8]

However, as measured by PSA, the association between obesity and bF after prostate cancer treatment remains controversial. Biochemical failure after EBRT was associated with increased BMI in several studies.[9–11] In a 10-year prospective study BMI had no association with bF or overall survival after RP.[12] Other studies confirmed an association with bF after RP.[13,14] Yet others showed that obesity does not predict bF after RP.[15,16] Retrospective analysis of Radiation Therapy Oncology Group 85-31 revealed that greater baseline BMI is associated with increased prostate cancer specific mortality after EBRT and AD therapy in men with locally advanced prostate cancer.[17]

These conflicting results may be explained by the fact that they did not include many factors that may be associated with bF after prostate cancer treatment. For example, these studies did not account for factors such as comorbidity and socioeconomic status.[9,11–13] Patient general health and socioeconomic status may be associated with prostate cancer specific mortality.[18] However, it is unclear whether bF is associated with patient characteristics, including comorbidity and socioeconomic status. Also, many studies of BMI as a predictor of bF included patients treated with a single modality.[9–16]

These previous groups did not look at the impact of BMI along with other possible confounders on bF after prostate cancer treatment with EBRT, RP or PB. We determined the association between BMI and bF in men treated for low and intermediate risk prostate cancer with EBRT, RP or PB.

MATERIALS AND METHODS

All patients treated for prostate adenocarcinoma between January 1996 and December 2005 at Cleveland Clinic were included in this cohort study. Patients are part of an institutional review board approved prostate cancer registry at Cleveland Clinic. Patients were included in study if they had at least 4 PSA screening tests and 2 years of PSA followup after PB, RP or EBRT and low or intermediate risk prostate cancer according to National Comprehensive Cancer Network guidelines, defined as low risk—T1 to T2a, Gleason score between 2 and 6, and serum PSA less than 10 ng/ml, and intermediate risk—T2b to T2c, Gleason score 7 or PSA 10 to 20 ng/ml.[19] The study end point was bF, as defined by a PSA increase of 2 ng/ml or greater from a posttreatment nadir for radiation modalities and PSA 0.4 ng/ml or higher after surgery.

RP may have been done as a laparoscopic or an open procedure. PB was done using an operating room based plan. EBRT was done as IMRT or nonIMRT and no patient had radiotherapy to nodal regions.

Race was coded as black or nonblack. Household income was calculated from United States Census data based on patient domicile ZIP Code™. Medical history, including age, smoking status, alcohol use, comorbidity (coronary artery disease, hypertension, dyslipidemia and hypothyroidism) and clinical/pathological information (clinical stage, initial and followup PSA, Gleason score and AD treatment) were extracted from patient medical records. A Charlson score was calculated based on patient comorbidity.[20] Height and weight were measured before prostate cancer treatment. BMI was analyzed as a continuous and a categorical variable. As a categorical variable, BMI was classified into 3 WHO designated categories, including normal—between 18.5 and 24.99 kg/m^2, overweight—25 to 29.99 kg/m^2 and obese—30 kg/m^2 or greater. Age, Charlson score, initial PSA, household income, smoking pack-years and the frequency of followup PSA testing were analyzed as continuous variables. Clinical staging was based on American Joint Committee on Cancer, 6th edition guidelines with cases categorized as T1–T2a or T2b–T2c.[21] Biopsy Gleason score was divided into well differentiated—6 or less and poorly differentiated—7.

Statistical analysis was done with StatView®, version 5.0 and SAS®, version 9.1. Differences in patient characteristics by BMI category were evaluated by 1-way ANOVA for continuous variables and the chi-square test for categorical variables. Kaplan-Meier curves were used to evaluate the biochemical failure risk based on BMI as a categorical variable. The log rank test was used to determine significant differences among BMI categories. To determine the time specific bFFS rate we performed actuarial analysis. The effect of various patient clinical and treatment characteristics on bF was analyzed using Cox proportional hazards univariate and multivariate regression analyses. The final multivariate model was constructed using the forward stepwise procedure. Variables were included in the multivariate model if they were statistically significant in the univariate model. Two-sided p values were calculated with $p \leq 0.05$ considered statistically significant.

RESULTS

Between January 1996 and December 2005 at Cleveland Clinic 6,075 consecutive men underwent treatment for prostate adenocarcinoma, of whom 2,687 met study criteria with respect to PSA followup and prostate cancer risk group. Of the patients 1,853 were excluded from study due to high risk disease and 1,535 were excluded due to insufficient PSA followup. Of the 2,687 study patients 595 (22.1%) were normal weight, 1,355 (50.4%) were overweight and 737 (27.4%) were obese. A total of 867 (32.3%), 1,199 (44.6%) and 621 men (23.1%)