Is There a Role for Body Mass Index in the Assessment of Prostate Cancer Risk on Biopsy?

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Abbreviations and Acronyms

AA = African-American

BMI = body mass index

bmiPCPTRC = BMI adjusted Prostate Cancer Prevention Trial prostate cancer risk calculator

DRE = digital rectal examination

HGPCa = high grade prostate cancer

PCa = prostate cancer

PCPT = Prostate Cancer Prevention Trial

PCPTRC = PCPT prostate cancer risk calculator

PSA = prostate specific antigen

SELECT = the Selenium and Vitamin E Cancer Prevention Trial

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Purpose: We examine the role of body mass index in the assessment of prostate cancer risk.

Materials and Methods: A total of 3,258 participants who underwent biopsy (including 1,902 men with a diagnosis of prostate cancer) were identified from the Selenium and Vitamin E Cancer Prevention Trial. The associations of body mass index with prostate cancer and high grade prostate cancer were examined using logistic regression, adjusting for age, race, body mass index adjusted prostate specific antigen, digital rectal examination, family history of prostate cancer, biopsy history, prostate specific antigen velocity, and time between study entry and the last biopsy. The prediction models were compared with our previously developed body mass index adjusted Prostate Cancer Prevention Trial prostate cancer risk calculator.

Results: Of the study subjects 49.1% were overweight and 29.3% were obese. After adjustment, among men without a known family history of prostate cancer, increased body mass index was not associated with a higher risk of prostate cancer (per one-unit increase in logBMI OR 0.83, p=0.54) but was significantly associated with a higher risk of high grade prostate cancer (ie Gleason score 7 or greater prostate cancer) (OR 2.31, p=0.03). For men with a known family history of prostate cancer the risks of prostate cancer and high grade prostate cancer increased rapidly as body mass index increased (prostate cancer OR 3.73, p=0.02; high grade prostate cancer OR 7.95, p=0.002). The previously developed risk calculator generally underestimated the risks of prostate cancer and high grade prostate cancer.

Conclusions: Body mass index provided independently predictive information regarding the risks of prostate cancer and high grade prostate cancer after adjusting for other risk factors. Body mass index, especially in men with a known family history of prostate cancer, should be considered for inclusion in any clinical assessment of prostate cancer risk and recommendations regarding prostate biopsy.

Key Words: prostatic neoplasms, prostate-specific antigen, body mass index, risk factors, neoplasm grading

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THE relationship between obesity (measured by body mass index) and prostate cancer has been studied extensively.[1–3] Obesity has been consistently linked to higher PCa mortality.[4,5] However, the relationship between obesity and risk of PCa is unclear, with individual studies showing conflicting results.[2,5–7] The inconsistency among individual studies might be due to differential effects of obesity on different tumor subtypes (localized/nonaggressive vs advanced/aggressive).[8] In particular, obese men have been observed to have lower concentrations of free testosterone which, in turn, were observed to be associated with a decreased risk of localized/nonaggressive PCa and with an increased risk of advanced/aggressive PCa.[9–13]

In a recent meta-analysis involving prospective studies on BMI and the risk of PCa separately by disease subtype, a decreased risk of localized PCa and an increased risk of advanced PCa were confirmed.[14] Confounding these conclusions, several studies have shown that higher BMI is associated with decreased serum PSA, potentially masking PCa detection including the detection of high grade PCa.[15–19] Therefore, the observed protective effects of BMI on the risk of PCa may be an artifact of hemodilution of PSA concentrations in obese men.[2,20] Recently we developed a BMI adjusted PCPT prostate cancer risk calculator that predicts all PCa risk as well as high grade PCa risk (Gleason score 7 or greater), while accounting for the effect of BMI on PSA using BMI adjusted PSA.[18] However, the usefulness of this risk calculator has not been externally validated.

We report on a study of PCa detection using SELECT,[21] with the goals of 1) conducting the first external validation for the bmiPCPTRC in a large cohort of healthy PSA screened biopsy confirmed men in North America, and 2) examining the associations of BMI with screen detected PCa as well as with HGPCa after adjusting for other risk factors.

MATERIALS AND METHODS

Subjects

SELECT is the largest PCa prevention trial performed, with 35,534 participants recruited and randomized between August 22, 2001 and June 24, 2004 from more than 400 sites throughout the United States, Puerto Rico and Canada.[21] Men eligible to join the study were age 55 years or older or, in the case of African-American men, age 50 or older; did not have a DRE suspicious for cancer; and had a PSA of 4 ng/ml or less. During annual clinic visits the participants were recommended to undergo a PSA test and DRE according to the standard of care at the study site and participant preference. Study supplementation ended on October 23, 2008, at which point the median overall followup was 5.46 years (range 4.17 to 7.33).

From 35,534 SELECT participants we identified 4,721 who had undergone prostate biopsy. For patients who underwent more than 1 biopsy, the results of the most recent biopsy were used to assess the effect of prior negative biopsy findings. PSA and DRE were measured at or within 1 year before the date of the most recent biopsy. For those with multiple PSA measurements longitudinally, PSA velocity was calculated by linear regression using all available PSA values measured from study entry to the date of the last biopsy. This was dichotomized as 1 if PSA velocity was greater than 0.35 ng/ml per year and 0 otherwise as recommended by the clinical guidelines by the National Comprehensive Cancer Network and the American Urological Association, and used by other researchers.[22] Age and BMI were collected at the date of the most recent biopsy. BMI adjusted PSA was calculated by multiplying the most recent PSA by 1.09, 1.20, 1.50 and 1.71 for men in overweight (BMI 25 to less than 30 kg/m^2), obese I (BMI 30 to less than 35 kg/m^2), obese II (BMI 35 to less than 40 kg/m^2) and obese III (BMI 40 kg/m^2 or greater) categories, respectively.[18] Information on race/ethnicity and first-degree family history of PCa was collected at study entry.

We also evaluated the duration of observation based on the time from study entry to the date of the last biopsy. Patients were excluded from analysis if they were current or past finasteride users (849), or had missing PSA, DRE or BMI at or within 1 year before the date of the most recent biopsy (614). The final sample size was 3,258 men, including 1,902 with a diagnosis of PCa and 1,356 without cancer (fig. 1). Compared with the 3,258 men included in the final analysis, the 614 who were excluded due to missing PSA, DRE or BMI had similar distributions in age, race, family history and HGPCa rate, although they had a higher prior negative biopsy rate (30.1% vs 20.9%, $p < 0.001$) and lower PCa rate (13.4% vs 58.4%, $p < 0.001$). This study was approved by the institutional review board at the University of Texas Health Science Center at San Antonio.

Statistical Analyses

Patient characteristics of those with a confirmed diagnosis of PCa were compared to the subjects without a PCa diagnosis using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Calibration of the bmiPCPTRC was assessed using calibration plots. In addition, the average PCa and HGPCa risks based on the bmiPCPTRC were compared to observed PCa and HGPCa rates, respectively, for the sample as a whole as well as among subgroups of PSA (less than 4 vs 4 ng/ml or greater), DRE (normal vs abnormal), age (65 years or older vs younger than 65), family history of PCa (yes vs no), BMI category (less than 25 vs 25 to less than 30 vs 30 kg/m^2 or greater) and race (white vs AA vs nonAA Hispanic). Diagnostic performance of the bmiPCPTRC was evaluated using the AUC. The difference between 2 AUCs was tested using the Z-statistic for comparing the usefulness of bmiPCPTRC between 2 independent subgroups.[23,24]

To assess the independent predictive effect of BMI on PCa and HGPCa, multivariate logistic regression was performed adjusting for other potential risk factors. A