

The Effects of Body Mass Index on Changes in Prostate-Specific Antigen Levels and Prostate Volume Over 15 Years of Follow-up: Implications for Prostate Cancer Detection

Lauren P. Wallner^{1,2}, Hal Morgenstern^{2,3}, Michaela E. McGree⁴, Debra J. Jacobson⁴, Jennifer L. St. Sauver⁵, Steven J. Jacobsen⁶, and Aruna V. Sarma^{1,2}

Abstract

Objective: To investigate the association of body mass index (BMI) and BMI change with change in prostate-specific antigen (PSA) level and to assess the possible roles of PSA hemodilution and prostate volume in explaining the obesity and PSA association.

Methods: In 1990, a randomly selected cohort of Caucasian men, aged 40 to 79 years, from Olmsted County, Minnesota, completed questionnaires ascertaining demographic characteristics, current medical conditions, and medications biennially, with a subset undergoing blood draws and clinical examinations. Linear mixed models were used to predict annual changes and intercepts of individual changes in BMI, PSA, prostate volume, plasma volume, and PSA mass, adjusting for age in 545 men with at least 2 serial PSA, BMI, and prostate volume measurements.

Results: Baseline BMI was inversely associated with the annual percent change in PSA, adjusting for age, baseline PSA, and prostate volume and for the rates of change in BMI and prostate volume ($\beta = -0.003$, 95% CI: -0.006 to -0.0003). Baseline obesity was positively associated with mean baseline levels and the rate of change in prostate volume ($P = 0.002$) and plasma volume (both $P < 0.001$) but was not associated with either the mean baseline values or the rate of change in PSA mass.

Conclusions: Baseline obesity was associated with baseline PSA and prostate volume and with the rate of change in PSA over 15 years of follow-up.

Impact: The inverse association of obesity with prostate cancer diagnosis may be at least partly due to detection bias, which is due to larger prostate volumes and PSA hemodilution in obese men. *Cancer Epidemiol Biomarkers Prev*; 20(3); 501–8. ©2011 AACR.

Background

Prostate cancer is the most common noncutaneous cancer in U.S. men, with an estimated 192,280 new cases diagnosed in 2009 (1). Prostate-specific antigen (PSA) currently is the most common screening test for prostate cancer, with 58% of Caucasian men receiving an annual test (2). The low specificity of PSA testing and questionable benefits of PSA screening on prostate cancer mortality highlight the need for better detection strategies for

prostate cancer (3). Knowledge of the influence of concomitant comorbidities on serum PSA concentrations may improve the discriminant value of this test for predicting prostate cancer and reduce the number of unnecessary biopsies and subsequent overdiagnoses of indolent cancers.

Obesity is a growing global epidemic, with more than half of the world's adults categorized as being overweight and up to 30% categorized as obese [body mass index (BMI) ≥ 30 kg/m²; ref. 4]. In the United States, 68% of adults are overweight or obese (5). Obesity may influence the detection of prostate cancer through prostate cancer screening (6, 7), specifically by influencing PSA levels and prostate volumes. Obese men have lower PSA levels than do nonobese men (7–9), which may be due to decreased testosterone concentrations (6) and/or plasma hemodilution, that is, the dilution of soluble tumor markers by increased plasma volumes (9). In addition, previous studies suggest that obese men are more likely to have a diagnosis of later-stage disease and less likely to have a diagnosis of early-stage disease (10–12), implying that the consequences of the role of prostate volume in this

Authors' Affiliations: Departments of ¹Urology and ²Epidemiology, ³Environmental Health Sciences and Comprehensive Cancer Center, University of Michigan, Ann Arbor, Michigan; Divisions of ⁴Biomedical Statistics and Informatics and ⁵Epidemiology, Mayo Clinic College of Medicine, Rochester, Minnesota; and ⁶Division of Research and Evaluation, Kaiser Permanente Southern California, Pasadena, California

Corresponding Author: Lauren P. Wallner, Department of Research and Evaluation, Kaiser Permanente Southern California, 3rd Floor, Pasadena CA 91104. Phone: 626-564-7663, Fax: 626-564-3409 E-mail: lauren.p.wallner@kp.org

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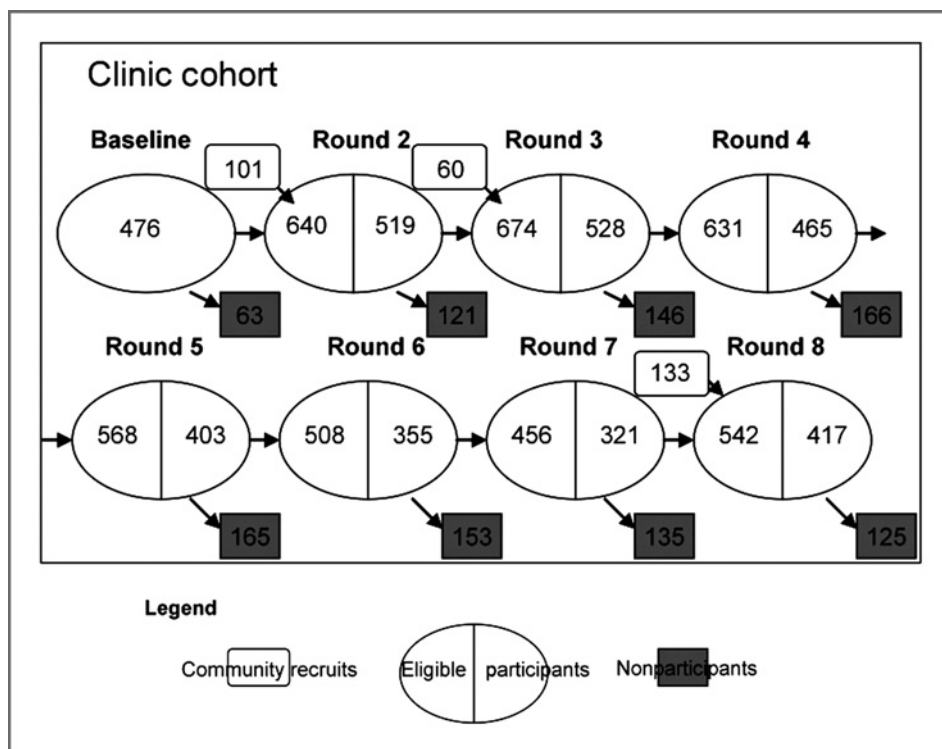


Figure 1. The OCS participation over time.

detection issue among obese men have important implications in terms of prostate cancer aggressiveness. Therefore, it is possible that obese men are less likely to be recommended for biopsy so that diagnoses may be delayed, resulting in later-stage disease at diagnosis and thus detection of fewer cancers in this group.

Results from previous studies suggesting that obesity may be associated with lower serum PSA concentrations are limited by their cross-sectional designs, their failure to simultaneously account for other aspects of this potential detection bias, including prostate volume, and their inability to elucidate why this association exists. Furthermore, the estimated effects of baseline obesity and weight change on change in serum PSA level and prostate volume in a population-based setting are limited. Understanding these longitudinal associations is relevant because change in serum PSA level may be better than a single serum PSA measurement for prostate cancer screening (13) and therefore has important implications for prostate cancer detection. The increasing prevalence of obesity coupled with the increasing speculation regarding the reliable detection of prostate cancer with serum PSA levels makes it crucial to elucidate how obesity influences the multiple facets of prostate cancer detection over time. Therefore, the goal of this study was to use longitudinal data to investigate the associations between BMI and change in BMI with change in PSA level and to assess the possible roles of PSA hemodilution and prostate volume in explaining the associations of obesity with PSA level and prostate cancer diagnosis.

Methods

Study population

The Olmsted County Study (OCS) of Urinary Symptoms and Health Status among Men is a longitudinal study of Caucasian men residing in Olmsted County, Minnesota (14, 15). In 1990, a random sample of men aged 40 to 79 years, as enumerated by the Rochester Epidemiology Project, was screened for inclusion (16). Men with a history of prostate or bladder surgery, urethral surgery or stricture, or medical or neurologic conditions that affect normal urinary function were excluded. Eligible men ($n = 3,874$) were invited to take part in the study, and 2,115 (55%) agreed to participate. Participants completed a previously validated baseline questionnaire that ascertained information on urinary symptoms, medical histories, and various demographic and behavioral characteristics. A 25% random subset of the total cohort was invited to participate in a detailed urologic clinical examination, which included prostate volume and serum PSA measurements. Of the 537 randomly selected men, 476 (89%) agreed to participate in the clinical portion of the study.

Since 1990, the cohort has been actively followed biennially by using a questionnaire similar to the one used at baseline. During the second and third rounds of visits, men who did not participate in the follow-up were replaced by randomly selected eligible men from the community ($n = 332$ total cohort; $n = 159$ clinic cohort; Fig. 1). After the third round, the study has been

maintained as a fixed cohort. Of the 2,447 men in the OCS, 634 men participated in the clinic cohort with up to 8 rounds of follow-up. Overall, 552 (87%) men had at least 2 PSA, BMI, and prostate volume measurements. All data up to the point of diagnosis or initiation of surgical or medical therapy for benign prostatic hyperplasia (BPH) were included in the analyses. Measurements of PSA level, prostate volume, plasma volume, and PSA mass were censored after diagnosis of prostate cancer, prostate surgeries, and procedures and use of any medications (prescription and herbal) for treatment of BPH. A total of 122 men had at least 1 observation censored. As a result, 545 men were included in this analysis.

Measurements

Measurements of BMI, prostate volume, and PSA were collected at each round of follow-up during the clinic examination. A trained research assistant measured height and weight, and BMI was calculated by dividing the weight in kilograms by the height in meters squared. Men with a BMI of 30 kg/m² or more were considered obese, based on the definition established by the World Health Organization (WHO; ref. 17). Prostate volume was measured via transrectal sonographic imaging, and serum PSA levels were determined with the Tandem-R PSA assay (Hybritech Inc.). To investigate what role plasma hemodilution plays in influencing PSA levels among obese men, body surface area, plasma volume, and PSA mass were estimated using the following established formulas: body surface area (m²) = body weight (kg)^{0.425} × height (m)^{0.725} × 0.2025 (18), plasma volume (L) = body surface area (m²) × 1.670 (19), and PSA mass = PSA (ng/mL) × plasma volume (9). Demographic information including salary, years of education, and age at baseline blood draw were collected using the questionnaire.

Statistical analysis

The cross-sectional associations between baseline obesity and participant demographics at baseline were tested using χ^2 tests for association and 2-sided Student's *t* tests where appropriate. The distributions of baseline values and predicted rates of change of PSA, BMI, and prostate volume were determined overall and across 10-year age groups, using medians and interquartile ranges. The associations of both the baseline values and predicted rates of change with age were tested using the test for trend from linear regression.

A longitudinal 2-step analytic approach was used to examine the associations of the individual intercepts and rates of change of BMI and prostate volume with the annual percent change in PSA. First, the rates of change in PSA, BMI, and prostate volume were estimated by individually regressing each measure on time from initial blood draw and age (10-year categories), using linear mixed-effects regression models. Interaction (product) terms were included to allow for different slopes across these age groups. Fixed and random effects were

included both to reflect the mean effect and to allow for individual variation in the baseline intercept and change over time. An overall annual change in each measure for each man was estimated by combining the average change over time (fixed effects) with the individual changes (random effects). Similarly, both fixed and random effects allowed determination of an overall baseline intercept for each age decade and for offsets for individual variation. Because of their skewed distributions, PSA level and prostate volume were natural log-transformed and therefore parameter estimates represent percent changes per year. The change in BMI reflects annual absolute changes.

The second step of this approach was to estimate the effects of predicted intercepts of PSA, BMI, and prostate volume and the predicted annual changes of BMI and prostate volume on the predicted annual percent change in PSA (all derived from the mixed model in step 1), using linear regression models adjusting for age.

Additional models of changes in PSA and prostate volume included a categorical measure for obesity (BMI < 30 kg/m²; BMI ≥ 30 kg/m²) and an interaction (product) term between obesity and time to compare the slope of PSA among those who were obese and those who were not obese. Similar models considered baseline BMI (treated as continuous), baseline BMI based on the WHO classifications, and repeated measures of BMI. Finally, to assess a possible delayed effect of BMI on PSA change, these additional models were rerun lagging PSA measures. Because measurements were collected biennially, PSA measures were lagged 2 years after the BMI measures.

The adjusted predicted values of the intercepts and annual changes of plasma volume and PSA mass were also estimated using linear mixed-effects regression models. Because of the skewed distribution, PSA mass was natural log-transformed and therefore parameter estimates represent percent changes per year. The change in plasma volume reflects annual absolute changes. The means and SDs of the predicted intercepts and annual changes of PSA mass and plasma volume from the mixed models were then compared across levels of age and baseline obesity. All statistical analyses were done using SAS 9.2 software (SAS Institute).

Results

Baseline characteristics of the study participants are shown in Table 1. Age was inversely associated with obesity at baseline ($P_{\text{trend}} = 0.03$), but marital status, education, salary, and prostate volume differed little by baseline obesity status (Table 1). Obese men more often reported a history of type 2 diabetes and a history of hypertension than did nonobese men at baseline ($P = 0.006$ and 0.008 , respectively). Men who were obese had a lower mean PSA level (1.1 ng/mL) than did men who were not obese at baseline (1.4 ng/mL; $P = 0.06$; Table 1).

Table 1. Participant baseline characteristics by baseline obesity status in 545 men

Baseline (1990) characteristic	Nonobese (BMI < 30 kg/m ² ; N = 404)	Obese (BMI ≥ 30 kg/m ² ; N = 141)	P ^a
Age, y			
40–49	163 (40.4)	69 (48.9)	0.03
50–59	104 (25.7)	39 (27.7)	
60–69	82 (20.3)	19 (13.5)	
70+	55 (13.6)	14 (9.9)	
Marital status			
Single, divorced, widowed, separated	41 (10.1)	11 (7.8)	0.41
Married/living together	361 (89.4)	130 (92.2)	
Education			
Less than high school graduate	39 (9.7)	19 (13.5)	0.18
Finished high school/some college	184 (45.5)	71 (50.3)	
College degree and beyond	178 (44.1)	51 (36.2)	
Salary			
<\$25,000	66 (16.3)	27 (19.1)	0.52
\$25,000–\$44,999	109 (27.0)	33 (23.4)	
\$45,000–\$64,999	109 (27.0)	36 (25.5)	
\$65,000+	97 (24.0)	42 (29.8)	
Diabetes			
No	392 (97.0)	129 (91.5)	0.006
Yes	12 (3.0)	12 (8.5)	
Hypertension			
No	310 (76.7)	92 (65.2)	0.008
Yes	94 (23.3)	49 (34.8)	
PSA, ng/mL			
Mean (SD)	1.4 (1.4)	1.1 (1.1)	0.06 ^b
Prostate volume, mL			
Mean (SD)	27.8 (11.8)	29.6 (12.9)	0.14 ^b

^aP value from χ^2 test for association.

^bP value from 2-sided Student's *t* test.

Table 2 displays the overall and age-specific distributions of the observed baseline values and predicted annual rates of change for BMI, PSA, and prostate volume (derived from the mixed models). At baseline, the median BMI in the total sample was 27.03 kg/m² and it was inversely associated with age ($P_{\text{trend}} = 0.07$). Both PSA and prostate volume at baseline were strongly and positively associated with age ($P_{\text{trend}} < 0.0001$). The median rate of change in BMI was 0.14 kg/m² per year, and it was inversely, though not monotonically, associated with age ($P_{\text{trend}} = 0.001$). The median rate of change of PSA was 3.82% per year, and this rate increased with age ($P_{\text{trend}} < 0.0001$). The median rate of change in prostate volume overall was 2.19% per year, and it was minimally associated with age (Table 2).

Table 3 summarizes the means and SDs of the predicted intercepts and annual percent changes in PSA and prostate volume by baseline obesity status. Baseline obesity (BMI ≥ 30 kg/m²) was weakly and inversely associated with baseline PSA levels adjusting for age ($P = 0.25$). Similar associations were observed with continuous

baseline BMI and BMI categorized according to the WHO classifications (Table 3). Men who were obese at baseline had a slightly lower age-adjusted mean annual percent change in PSA level than did men who were not obese (3.04 vs. 3.79; $P = 0.33$). Baseline obesity was positively associated with baseline prostate volume ($P = 0.002$) and this association was similar when assessed using baseline BMI and categorical BMI based on WHO classifications (Table 3). Men who were obese at baseline had slightly higher mean annual percent change in prostate volume than did men who were not obese (2.48 vs. 2.20; $P = 0.27$). The association between baseline obesity and annual percent change in PSA did not change when repeated measurements of BMI were modeled and when PSA measurements were lagged 2 years after the measurement of obesity ($\beta = -0.05$; 95% CI: -0.17 to 0.08).

In multivariable models considering the association of predicted annual percent change in PSA with the predicted intercepts of PSA, prostate volume, and BMI and the rates of change of prostate volume and BMI, baseline BMI was inversely associated with the rate of change in

Table 2. Overall and age-stratified medians and interquartile ranges of observed baseline and predicted rate of change for BMI, PSA, and prostate volume

	Median (Q1–Q3)					<i>P</i> ^a
	Overall	40–49 y	50–59 y	60–69 y	70+ y	
Observed baseline value						
BMI, kg/m ²	27.03 (24.97–30.05)	27.1 (24.90–30.35)	27.72 (25.09–30.09)	26.56 (24.75–28.99)	26.52 (24.99–28.90)	0.07
PSA, ng/mL	0.9 (0.60–1.50)	0.7 (0.50–1.05)	0.9 (0.60–1.40)	1.4 (0.80–2.60)	2 (1.00–3.10)	<0.0001
Prostate volume, mL	25.57 (20.30–32.63)	21.27 (18.69–26.01)	27.5 (22.32–33.06)	31.46 (24.81–38.20)	32.92 (25.66–44.90)	<0.0001
Predicted rate of change						
BMI (change/y)	0.14 (0.07–0.19)	0.16 (0.10–0.22)	0.14 (0.08–0.19)	0.06 (0.02–0.09)	0.17 (0.13–0.19)	0.001
PSA (% change/y)	3.82 (1.58–5.64)	2.43 (0.62–4.32)	4.39 (2.24–6.05)	4.81 (3.16–6.45)	5.07 (3.30–6.08)	<0.0001
Prostate volume (% change/y)	2.19 (1.67–2.83)	2.26 (1.72–2.83)	2.14 (1.62–2.74)	2.15 (1.75–2.85)	2.17 (1.56–2.99)	0.93

^aTest for trend across age groups.

PSA ($P = 0.03$). Age, baseline PSA level, and annual percent change in prostate volume were also positively associated with annual percent in PSA when mutually adjusted for the other covariates ($P = 0.04$, < 0.0001 , and < 0.0001 , respectively). Further adjustment for baseline statin and nonsteroidal anti-inflammatory drug use did not change the results (data not shown).

Table 4 summarizes the means and SDs of the predicted intercepts of and rates of change in plasma volume and

PSA mass, by 10-year age category and baseline obesity status. Men who were obese at baseline had a higher age-adjusted mean plasma volume level at baseline (3.69 L) than did men who were not obese (3.33 L) ($P < 0.001$). Men who were obese at baseline also experienced a smaller annual change in plasma volume (0.001 L/y) than did men who were not obese (0.005 L/y; $P < 0.001$). Neither baseline levels nor the rate of change in PSA mass differed across baseline obesity status, adjusting for age (both $P > 0.20$).

Table 3. Mean and SDs of adjusted predicted intercepts and annual percent change of PSA and prostate volume by baseline obesity measures

Baseline characteristic	<i>N</i>	PSA intercept	Annual percent change in PSA	Prostate volume intercept	Annual percent change in prostate volume
BMI, kg/m ² (continuous)	545	−0.02 (0.68)	3.59 (3.03)	3.27 (0.32)	2.28 (1.03)
<i>P</i>		0.18	0.16	0.004	0.46
Obesity					
BMI < 30 kg/m ²	404	0.01 (0.69)	3.79 (2.88)	3.25 (0.32)	2.20 (1.01)
BMI ≥ 30 kg/m ²	141	−0.13 (0.64)	3.04 (3.37)	3.30 (0.33)	2.48 (1.09)
<i>P</i>		0.25	0.33	0.002	0.27
BMI (WHO cutoffs)					
<25 kg/m ²	141	−0.04 (0.72)	3.89 (2.89)	3.20 (0.29)	2.29 (0.98)
25–29 kg/m ²	263	0.04 (0.67)	3.74 (2.87)	3.28 (0.33)	2.16 (1.03)
30–34 kg/m ²	115	−0.09 (0.66)	3.37 (3.38)	3.32 (0.34)	2.46 (1.11)
35+ kg/m ²	26	−0.31 (0.45)	1.35 (3.07)	3.24 (0.25)	2.62 (1.02)
<i>P</i>		0.4	0.45	0.002	0.7

NOTE: All models are adjusted for age, and both PSA level and prostate volume are natural log-transformed.

Table 4. Mean and SDs of the adjusted predicted intercepts and rates of change of plasma volume and PSA mass by age category and baseline obesity status

Baseline characteristic	Plasma volume intercept	Annual change in plasma volume	PSA mass intercept	Annual percent change in PSA mass
Overall ^a	3.43 (0.27)	0.004 (0.007)	1.21 (0.67)	3.56 (2.95)
<i>P</i>	<0.001	0.002	<0.001	<0.001
Age, y				
40–49	3.48 (0.29)	0.008 (0.006)	0.95 (0.49)	2.79 (2.89)
50–59	3.45 (0.25)	0.005 (0.005)	1.14 (0.59)	4.23 (3.06)
60–69	3.35 (0.24)	–0.002 (0.005)	1.59 (0.69)	4.38 (2.87)
70+	3.28 (0.24)	–0.002 (0.006)	1.71 (0.83)	3.70 (2.36)
<i>P</i>	<0.001	<0.001	<0.001	0.05
Baseline obesity ^a				
BMI < 30 kg/m ²	3.33 (0.22)	0.005 (0.007)	1.22 (0.69)	3.77 (2.83)
BMI ≥ 30 kg/m ²	3.69 (0.23)	0.001 (0.008)	1.17 (0.62)	2.95 (3.23)
<i>P</i>	<0.001	<0.001	0.79	0.23

^aAdjusted for age.

Discussion

In this longitudinal study of Caucasian men aged 40 to 79 years, those with higher baseline BMIs had lower baseline PSA levels and less rapid increases in PSA over time. Baseline obesity was also associated with increased plasma volume at baseline and the age-adjusted rate of change in plasma volume over time. Our results suggest that higher BMI is associated with lower PSA levels and less rapid increases in PSA level, purportedly through hemodilution effects. These findings suggest that men with higher BMIs may be less likely to be screened for prostate cancer because of consistently lower PSA levels over time.

Previous cross-sectional studies have shown that obese men have lower PSA levels than do nonobese men (9, 20, 21), which may result in fewer prostate biopsies among obese men. Our finding that baseline BMI was inversely associated with baseline PSA level is similar to those previous cross-sectional findings (8, 21, 22). Furthermore, our results suggest that baseline obesity is also inversely associated with how rapidly PSA levels increase over time. This finding is important, as the rate of change in PSA level or PSA velocity is currently the preferred measure used to diagnose prostate cancer (13, 23).

Our findings also suggest that the association between BMI and PSA is at least in part due to the hemodilution of PSA because baseline obesity was associated with increased plasma volume but not with baseline PSA mass (the product of PSA concentration and plasma volume). Similar associations were seen longitudinally, as baseline obesity was associated with the rate of change in plasma volume but not with the annual percent change in PSA mass over time. Our cross-sectional results are similar to previous studies that found plasma volume to increase

with increasing BMI but found no relation between BMI and PSA mass (9, 24). Our longitudinal findings are similar to the results from the placebo arm of the Prostate Cancer Prevention Trial that suggest that increased weight gain is inversely associated with change in PSA (25). Our findings further suggest that the hemodilution of PSA is in part responsible for the association of baseline BMI and changes in PSA over time, which is similar to those simulated previously that suggest both static obesity and weight gain attenuate PSA velocity over time (26). Taken together, these findings have important implications for prostate cancer screening and detection, as current prostate cancer screening practices that use cross-sectional or longitudinal measures of PSA without taking into account BMI may result in missed or delayed diagnoses due to obese men being less likely to be referred for biopsy.

Our results also support the notion that prostate cancer detection issues among obese men could be partly due to the influence of BMI on prostate volume. In this cohort, men with higher baseline BMIs had higher baseline prostate volumes. Our results are similar to several previous studies that found obese men to have larger prostates (7, 27). It is therefore possible that fewer cancers are then detected in obese men because of their larger prostate size or that the diagnoses are delayed, resulting in more aggressive disease at diagnosis.

Overall, the findings from our study, taken together with findings from previous studies, suggest that prostate cancer may be less likely to be detected in obese men partly due to the influence of BMI on the rate of prostate volume growth and the hemodilution of PSA. (7, 28) This bias, coupled with the findings that obese men present with later-stage disease (12) and have worse outcomes after treatment, including greater risk of recurrence

(29, 30), suggests that it may be appropriate to take into consideration the obesity status of a man when interpreting PSA screening results and recommending prostate biopsies. To minimize this detection bias, it may be prudent to lower PSA cutoffs for overweight or obese men and/or take more cores in these men at biopsy.

The strengths of this study include the use of longitudinal data with 15 years of follow-up that contained rigorously collected repeated measures of BMI, prostate volume, and serum PSA levels. Censoring outcome values collected after prostate cancer diagnosis, BPH treatment, or prostate surgery yields a disease-free, asymptomatic population. However, this study also has potential limitations that need to be considered. This cohort is composed entirely of Caucasian men, limiting our inferences to other racial and ethnic groups. The long follow-up period makes attrition inevitable; however, previous work in this cohort found that participant drop-out was not associated with chronic diseases or serum PSA levels adjusted for age (31), thus suggesting that bias resulting from attrition may be small. Finally, there may

have been unmeasured time-dependent confounders that we were unable to account for in our analyses.

In conclusion, baseline obesity was associated with baseline PSA and prostate volume and the rate of changes in PSA. Our results suggest that obesity may delay detection of prostate cancer due in part to larger prostate volumes and PSA hemodilution in obese men. Clinically, it may be prudent to lower PSA cutoff points for overweight or obese men and/or take more cores in these men at biopsy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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