Trends and Co-trends of Prostate-specific Antigen and Body Mass Index in a Screened Population

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OBJECTIVES
This report investigated whether annual changes in body mass index (BMI) are associated with the opposite changes in prostate-specific antigen (PSA). Previous studies have confirmed lower PSA levels among men with higher BMI.

METHODS
Normal linear mixed models were used to characterize annual PSA, BMI and the ratio of PSA to BMI profiles for 2641 men undergoing prostate cancer screening for up to 8 years as part of a San Antonio screening study.

RESULTS
Among the 1898 participants (71.9%) who never received a prostate biopsy during the study and the 585 participants (22.1%) who had one or more biopsies, all negative for prostate cancer, BMI was higher for Hispanics than other racial groups, lower for older men at study entry, and increased every year during the study; and PSA and PSA/BMI ratios were higher for older men at study entry and increased each year on study (all P values <.05). Among the 158 men (6.0%) eventually diagnosed with prostate cancer, no trends in BMI were statistically significant, but PSA and PSA/BMI ratios were higher on average for older men at study entry and increased each year on study (both P values <.05). Correlations between BMI and PSA changes per year were negative but not statistically significantly different from zero.

CONCLUSIONS
The individual man scrutinizing his PSA and weight year to year can expect a slight annual increase in both, but changes in PSA from one year to the next cannot be attributed to weight gain or loss.

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One in 6 men will be diagnosed with prostate cancer during their lifetime and 1 in 35 will die from the disease. In the United States, despite limitations in sensitivity and specificity, prostate-specific antigen (PSA) is commonly used for screening for prostate cancer and serves to identify men eligible for more intensive diagnostic procedures, such as prostate biopsy for men with PSA levels >4.0 ng/mL. It is now not uncommon for men to undergo annual screening and to be familiar with their own track record of PSA. In addition, at annual doctor visits, men are reacquainted with their weight and may also keep track of weight gains or losses. What is less recognized is the relationship between these 2 measures of health. Several studies have confirmed an inverse association between body mass index (BMI) and PSA, whereby obese men have lower PSA levels than nonobese men after controlling for other potential explanatory factors, including race and ethnicity.1-11 In other words, all other things being equal, an obese man may have a lower PSA than a nonobese man and may be less likely to exceed a threshold for referral to biopsy.12 These associations are cross sectional, comparing average correlations between PSA and BMI among different men of different weights. The purpose of this report was to report average annual changes in PSA and BMI among men undergoing contemporary screening for prostate cancer, with a particular focus on what a man who loses or gains weight can expect in terms of change in his own PSA.

MATERIAL AND METHODS
The San Antonio Center for Biomarkers of Risk of Prostate Cancer (SABOR) is an ongoing National Cancer Institute, Early Detection Research Network-sponsored clinical validation center enrolling community-dwelling men for annual prostate cancer screening performed by PSA and digital rectal examination (DRE). Earliest members of the cohort have been
followed for up to 10 years. Men are offered a prostate biopsy as part of the program if their annual PSA exceeds 2.5 ng/mL, their DRE examination is suspicious for prostate cancer, or, selectively, if they have a first-degree relative with prostate cancer. From this cohort, 2641 men who were enrolled through May 2009 and had at least one measure of PSA or BMI were identified for analysis. Of these 2641 men, 1898 (71.9%) never underwent prostate biopsy during the study period, 585 (22.1%) underwent prostate biopsy at least once with all biopsies negative for prostate cancer, and 158 (6.0%) underwent prostate biopsy at least once and were ultimately diagnosed with prostate cancer. Among participants who either never received a biopsy during the study or had one or more negative biopsies, all available annual PSA and BMI measures were analyzed; among participants diagnosed (cases), only annual measures before the time of diagnosis were analyzed. This resulted in a total of 8347 BMI measures and 9244 PSA measures for the 1898 participants who never received a prostate biopsy, 2986 BMI and 3283 PSA measures for the 585 participants who had one or more negative biopsies during the study, and 548 BMI and 648 PSA measures for participants diagnosed with prostate cancer. For analyses of longitudinal PSA-to-BMI ratios, only annual visits where both were recorded were used, resulting in a total of 5755 ratios for participants who never underwent biopsy, 1616 ratios for participants with one or more negative prostate biopsies, and 327 ratios for the participants who were diagnosed with prostate cancer. Age, race/ethnicity, first-degree family history of prostate cancer, and history of a prior negative biopsy were recorded for each participant.

Descriptive statistics were used to summarize participant characteristics, including age, PSA, BMI and the ratio of PSA to BMI at first visit, race/ethnicity, family history and prior negative biopsy history. Characteristics were compared among the 3 groups of participants (no biopsy, negative biopsy, and prostate cancer diagnosis) using analysis of variance for continuous measures after statistical diagnostics that assumptions of normal distributions for observations within groups were satisfied. For other categorical characteristics, contingency table analyses were performed using the chi-square test. Normal linear mixed models (NLMMs) were fit to natural logarithmically transformed ratios of PSA to BMI. A random effect structure was selected for all models comprised a random intercept and linear slope with time since enrollment. Normal probability plots were used to assess the normality assumption of within-subject residuals. Upon indenrollment. Normal probability plots were used to assess the normality assumption of within-subject residuals. Normal probability plots were used to assess the normality assumption of within-subject residuals. Upon incorporating a random intercept and linear slope with time since recruitment. Normal probability plots were used to assess the normality assumption of within-subject residuals.13 Upon indicating of potentially heavy tails in the residuals, all models were refit using generalized estimating equations, which do not rely on the normality assumption. The models gave nearly identical fits, standard errors, and P values to the NLMMs, so the results of the NLMMs were considered sufficiently robust to potential slight violations of normality and are reported in this analysis. Correlation and associated 95% confidence intervals (CIs) between random PSA and BMI slopes were estimated using bivariate NLMMs. All statistical tests were performed at the two-sided 0.05 level of statistical significance and conducted using the R statistical package (Version 2.9.0, Copyright 2009, R Foundation for Statistical Computing).

RESULTS

Characteristics of participants at study entry are summarized in Table 1. Participants with at least 1 biopsy performed during the study, including those eventually diagnosed with cancer, were statistically significantly older (median 62.3 and 62.1 years for the cancer cases and participants with at least 1 negative biopsy, respectively, compared with 57.0 years in participants who did not receive a biopsy during the study, P < .001) and had statistically significantly higher PSA values at entry to the study (median 1.8, 1.5, and 0.8 ng/mL for the 3 groups, respectively, P < .001). Although height at entrance to the study was constant across the 3 groups of participants stratified by their biopsy status, the group that never received a biopsy during the study weighed more (median 195 lb) than either cancer cases (median 192 lb) or men who subsequently underwent at least 1 biopsy during the study (median 190 lb) (P < .001). A higher proportion of men diagnosed with cancer were African American (15.2% compared with 14.0% and 9.1% in the no biopsy and negative biopsy groups, respectively, P < .0001) and men with a positive family history at study entry were more likely to have undergone biopsy during the study (P < .001). This latter effect is primarily a screening bias because as part of a family history substudy, SABOR participants with a positive family history were intermittently offered a prostate biopsy regardless of PSA and DRE findings during some of the study years. Participants diagnosed with prostate cancer were removed from the cohort upon detection and hence there were fewer years of follow-up for these men compared with those not diagnosed (P < .001).

Figure 1 shows the wide variation among BMI profiles and changes in the BMI distributions by year of study observed among the 3 groups of participants. Among the majority group of 1898 participants (71.9%) who never received a biopsy during the study, BMI was statistically significantly but only mildly lower for older men at study entry (0.13% lower for each increase in year of age, 95% CI .05-.21%, P = .001, Fig. 1) and statistically significantly higher among Hispanics compared with Caucasians (2.60% higher; 95% CI 0.94-4.29%, P = .015). African Americans had 2.12% higher BMI values on average compared with Caucasians, but the difference was not statistically significant (P > .05). BMI increased by 2.40% with each year on the study for all men who did not undergo prostate biopsy (95% CI 2.01-2.79%, P < .0001) and increased slightly less per year for older compared with younger men (increased less 0.04% per year on study for each increase in year of age to entry to the study, 95% CI 0.03-0.04%, P < .0001, Fig. 1). Among the second majority group of 585 participants (22.1%) who underwent at least 1 negative prostate biopsy during the study, similar trends were seen, but varied in effect size (Fig. 1). BMI was 0.21% lower for each increase in year of age at entry to the study (95% CI .08-.33%, P = .001) and was statistically signifi-
cantly higher among Hispanics and African Americans compared with Caucasians (4.96% higher; 95% CI 2.23-7.77%, and 4.50% higher; 95% CI 0.38-8.80%, respectively, *P* < .001). BMI increased only by 1.02% with year on study for these participants (95% CI 1.09-2.67%, *P* < .001) and increased slightly less per year for older compared with younger men (increased less 0.03% per year on study for each increase in year of age of entry to the study, 95% CI 0.02-0.04%, *P* < .0001). For the 158 (6.0%) participants diagnosed with prostate cancer, there were no statistically significant effects on BMI.

Figure 2 shows patterns of PSA for the 3 groups of participants where clear group differences are seen from

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cancer Cases (n = 158)</th>
<th>Participants Who Had No Biopsy (n = 1898)</th>
<th>Participants With at Least One Negative Biopsy (n = 585)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62.3 (39.8, 84.5)</td>
<td>55.6 (28.7, 88.5)</td>
<td>62.1 (33.7, 87.5)</td>
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<tr>
<td>Height (in)</td>
<td>70 (57, 78)</td>
<td>70 (51, 84)</td>
<td>70 (60, 79)</td>
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<tr>
<td>Weight (lb)</td>
<td>192 (142, 322)</td>
<td>195 (117, 420)</td>
<td>190 (115, 297)</td>
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<td>BMI (kg/m²)</td>
<td>27 (21, 46)</td>
<td>28 (17, 54)</td>
<td>27 (20, 45)</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>1.8 (0.2, 8.9)</td>
<td>0.8 (0.1, 9.6)</td>
<td>1.5 (0.1, 25)</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td>Hispanic</td>
<td>34 (21.5%)</td>
<td>Hispanic</td>
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<tr>
<td>Family history</td>
<td>No</td>
<td>115 (72.8%)</td>
<td>No</td>
</tr>
<tr>
<td>Number of years of follow-up</td>
<td>3.2 (0.9, 7.7)</td>
<td>5.3 (0.8, 8.2)</td>
<td>6.3 (0.9, 8.2)</td>
</tr>
<tr>
<td>Number of PSA measures</td>
<td>4 (2, 8)</td>
<td>5 (1, 11)</td>
<td>6 (0, 10)</td>
</tr>
<tr>
<td>Number of BMI measures</td>
<td>3 (0, 8)</td>
<td>4 (0, 9)</td>
<td>5 (0, 9)</td>
</tr>
<tr>
<td>Gleason grade</td>
<td>5</td>
<td>3</td>
<td>1.9%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>105</td>
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<tr>
<td></td>
<td>Missing</td>
<td>8</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

Statistics columns refer to the median (range) where the % is not indicated and the variables from age to family history refer to at the first annual visit.

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the association of PSA to referral to biopsy in the SABOR study (higher PSA distributions for men with one or more negative biopsies compared with men not referred) and association of PSA with prostate cancer (higher, rising PSA distributions among men ultimately diagnosed with prostate cancer compared with those not). For all 3 groups, only age of entry to the study and time in the study had statistically significant effects on PSA. PSA increased by 2.04%, 1.26%, and 1.31% for each increase in year of age of entry to the study for men with no biopsy during the study, men with at least 1 negative biopsy, and men diagnosed with prostate cancer, respectively (95% CI 1.74-2.34%, 0.51-2.02%, and 0.19-2.44%, respectively, P < .0001, P = .001, P = .02, respectively), and all 3 groups had a statistically significant increase in the PSA-to-BMI ratios per year of study (2.78% increase per year, 95% CI 2.24-3.33%; 2.54%, 95% CI 1.24-3.86%; and 11.91%, 95% CI 8.96-14.93%, respectively).

Finally, to address the question of whether changes observed in BMI over years on study were associated with changes in PSA over the years, correlations between individually estimated PSA and BMI trajectories were estimated by fitting joint NLMMs. For all 3 groups these correlations were estimated to be negative, but they were small in magnitude and not statistically significantly different from 0 (correlations = -0.049, -0.048, and -0.17 for participants with no biopsy, negative prostate biopsies, and cases diagnosed with prostate cancer, respectively; all P > .05).
COMMENT

In a study of men undergoing annual PSA screening as part of the Prostate Cancer Prevention Trial (PCPT), Etzioni et al observed that among a large cohort of 8620 men who did not develop prostate cancer during the 7 years of follow-up, PSA increased annually by 3%, which is nearly identical to the 2.97% average annual PSA increase observed among the 2483 men in this study who did not develop prostate cancer. In a study of 24,869 healthy Korean men with initial PSA <4.0 ng/mL, Ham et al observed an annual PSA increase of 0.02 ng/mL/year. The practical implications for the individual man undergoing active PSA screening for prostate cancer with serial testing is that he can expect his PSA to change as he ages and he may wish to consult his physician regarding the use of conventional age-adjusted PSA cutoff values. However, the magnitude of change in PSA value over time (with the PSA assay coefficient of variation near 3% for PSA levels <3.0 ng/mL) results in annual fluctuations of PSA that could overwhelm the effects of aging.

BMI slowly increases up until age 50-60 years, where a gradual decline occurs. Two explanations have been advanced to explain the lower levels of PSA among obese men: a hemodilution effect caused by greater blood volume or suppression of PSA production caused by lower testosterone levels and higher estrogen levels among obese men.

Whether and how an individual’s change in BMI relates to changes in PSA has been less well-studied, but one cohort study implicated the same negative association. In a study of 3341 placebo participants from the PCPT who were prostate cancer-free at the end of the study, Kristal et al noted a statistically significant negative association between weight change and percent change in PSA over 6 years on trial. Specifically, 10 lb of weight gain over a single year was statistically significantly associated with a 0.024 ng/mL drop in PSA over that year. Repetition of this analysis among the 2483 men in this study who did not develop prostate cancer revealed strikingly similar results: a statistically significant 0.029 ng/mL drop in PSA for a 10-lb weight gain over a single year. Although statistically significant, the magnitude of effect on PSA (<0.05 ng/mL) is negligible.

CONCLUSIONS

PSA is currently the ubiquitous tool for screening for prostate cancer and how or whether it remains so in the emerging climate of over-diagnosis will soon be realized. Currently, it is not uncommon for patients to scrutinize year-to-year fluctuations of PSA as small as 0.1 ng/mL, even though they fall within the measurement error of

Figure 2. Prostate-specific antigen distributions for participants who developed prostate cancer (black, n = 158); participants who underwent at least 1 prostate biopsy during the study, all negative for prostate cancer (gray, n = 585); and participants who never underwent prostate biopsy during the study (white, n = 1898) by year on study. Year 0 is at study entry and Year 6 includes all measurements at or beyond Year 6 of the study. Boxes range from the 25th to the 75th percentiles of the distribution with horizontal lines within the boxes denoting the median; whiskers extend from the edge of the box out to 1.5 times the interquartile range, and individual points beyond the whiskers are denoted by asterisks. Five points with PSA >15 ng/mL are omitted from the plot for clarity.
the assays that measure it. As a biological marker, PSA is influenced by many mechanisms other than prostate cancer, so alterations in PSA cannot be solely attributed to the disease. On the basis of data from a large prostate cancer screening study with annual follow-up, this report has confirmed prior findings of statistically significant inverse associations between PSA and BMI, and a finding observed from a single prior study, the PCPT, of a significant but negligible decrease in PSA among men who gained 10 lb in one year. However, the SABOR study experience has revealed no statistically significant correlation between weight changes and PSA changes for the average man undergoing annual screening for prostate cancer. In other words, men without prostate cancer who lose or gain weight over the years should not expect a corresponding respective noticeable increase or decrease in PSA.

References