Serum Prostate-Specific Antigen Hemodilution Among Obese Men Undergoing Screening in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

Robert L. Grubb III, 1 Amanda Black, 3,4 Grant Izmirlian, 2 Thomas P. Hickey, 5 Paul F. Pinsky, 3 Jerome E. Mabie, 5 Thomas L. Riley, 5 Lawrence R. Ragard, 6 Philip C. Prorok, 2 Christine D. Berg, 3 E. David Crawford, 7 Timothy R. Church, 8 and Gerald L. Andriole, Jr., 1 for the PLCO Project Team

1Division of Urologic Surgery, Washington University School of Medicine, St. Louis, Missouri; 2Biometry Research Group and Early Detection Research Group 3Division of Cancer Prevention, and Cancer Prevention Fellowship Program, Office of Preventive Oncology National Cancer Institute, NIH, Bethesda, Maryland; 4Information Management Services and Westat, Inc., Rockville, Maryland; 5University of Colorado Health Sciences Center, Denver, Colorado; and 6University of Minnesota, Minneapolis, Minnesota

Abstract

Background: Previous studies have shown an inverse relationship between prostate-specific antigen (PSA) concentration and body mass index (BMI). It has been recently proposed that this relationship may be explained by the larger plasma volume of obese men diluting a fixed amount of PSA (hemodilution effect). We examined this hypothesis in a cohort of men enrolled in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Methods: Of 38,349 men ages 55 to 74 years randomized in PLCO to receive annual PSA and digital rectal examination screening, 28,380 had a baseline PSA, complete demographic information, and no prostate cancer diagnosis within 6 years from baseline. Self-reported height and weight were used to calculate BMI and to estimate plasma volume. PSA mass was estimated as PSA concentration times plasma volume. Multivariable linear regression models were used to investigate the relationship between PSA concentration, plasma volume, PSA mass, and BMI.

Results: PSA concentration significantly decreased with increasing BMI (p < 0.001); mean PSA values were 1.27, 1.25, 1.18, and 1.07 ng/mL among normal (BMI, 18.5-25), overweight (BMI, 25-30), obese (BMI, 30-35), and morbidly obese (BMI, >35) men, respectively. However, plasma volume also increased with increasing BMI and PSA mass showed no association with BMI, with mean values of 3.78, 3.95, 3.97, and 3.82 mg across the four BMI categories (p = 0.10).

Conclusions: This study confirms earlier findings that the inverse relationship between PSA concentration and BMI may be explained by a hemodilution effect. These findings could have implications for prostate cancer screening in large men.

Introduction

Both obesity and prostate cancer are increasing health problems in the United States (1, 2). Epidemiologic data have not shown a consistent relationship between obesity and prostate cancer incidence (3). Several studies have suggested a more aggressive course of the disease and increased risk of mortality from prostate cancer in obese men (4, 5). There are several biological explanations for the potentially more aggressive nature of prostate cancer in obese men, but obesity also creates practical issues with screening and diagnosis (6, 7). One of these potential issues is the effect of obesity on serum prostate-specific antigen (PSA).

The inverse relationship between body mass index (BMI) and serum PSA levels has been established (8, 9). Investigators have proposed that this effect may be due to decreased testosterone levels in obese men (10, 11). Recently, however, researchers have proposed an alternative hypothesis—that the inverse relationship between BMI and serum PSA could be explained by hemodilution. Banez et al. (12), in a retrospective study of prostate cancer patients who had undergone radical prostatectomy, found that although PSA concentration decreased significantly with BMI, the estimated total PSA mass did not, suggesting that the lower PSA concentrations observed in overweight and obese men could be merely due to the fact that men with greater BMI also tended to have larger plasma volumes. Rundle and Neugut (13) confirmed the findings of Banez et al. (12) in a cohort of healthy employees undergoing annual physical exams.

Cancer Epidemiol Biomarkers Prev 2009;18(3):748–51
showing that estimated plasma volumes could be used to accurately predict mean PSA concentrations in obese and morbidly obese men. In this article, we sought to investigate whether the relationship of plasma volume and PSA was maintained in a large cohort of prostate cancer-free men enrolled in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial.

Patients and Methods

Setting and Participants. The PLCO Cancer Screening Trial is a multicenter, randomized, two-arm trial designed to evaluate the effect of screening for prostate, lung, colorectal, and ovarian cancer on disease-specific mortality. Randomization began in November 1993 and concluded in July 2001, with 154,942 men and women enrolled. 38,349 men were randomized to the intervention arm. The study design, methods, and exclusion criteria have been previously described (14). All participants signed informed consent documents approved by both the National Cancer Institute and local institutional review boards.

Men were included in the current analysis if they had a baseline PSA measurement and no diagnosis of prostate cancer for the following 6 years. In addition to data recorded at screening examinations, the following participant-reported data were collected at entry to the study on a baseline questionnaire: sociodemographic and educational information, behavioral and life-style factors, anthropometric details, personal medical history, and family history of prostate cancer. Specifically, height and weight were self-reported on the baseline questionnaire.

Clinical Variables. All baseline serum PSA concentrations (ng/mL) were measured in a single laboratory at University of California Los Angeles using a Hybritech Tandem-R assay (Beckman-Coulter). BMI was calculated from self-reported anthropometry as weight (kg)/height (m)^2. Body surface area, plasma volume, and PSA mass were estimated using the following established formulae:

1. Body surface area (m^2) = body weight (kg)^(0.425) x height (m)^(0.725) x 0.2025 (15)
2. Plasma Volume (L) = body surface area (m^2) x 1.670 (16)
3. PSA mass (µg) = PSA concentration x plasma volume (12)

PSA mass was defined as the total amount of PSA protein in circulation at the time of PSA concentration measurement. BMI was categorized according to the WHO’s thresholds for normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), obese (30.0-34.9 kg/m^2), and morbidly obese (≥35 kg/m^2; ref. 17).

Statistical Analysis. Cohort characteristics were compared across BMI categories using ANOVA for age as a continuous variable and χ^2 for all categorical variables. Multivariable linear regression was used to investigate the relationship between BMI and serum PSA concentration, plasma volume, and PSA mass. PSA concentration and mass were log transformed before entry into regression models; the estimates obtained were then back transformed for ease of interpretation. To test for trends in PSA concentration, plasma volume, and PSA mass across categories of BMI, BMI groupings were entered as a continuous variable and the Wald test of the coefficient assessed. Fully adjusted models included age (years), race (Black, White, other), family history of prostate cancer (yes/no), history of prostate problems (yes/no), year of screen, and study center.

Results

Cohort Characteristics. Of the original 38,349 men randomized to the intervention arm, 29,546 had a valid baseline PSA measurement and had not been diagnosed with prostate cancer within the following 6 years. Men were excluded from analyses if data on main analysis variables or covariates were missing: BMI (n = 452), race (n = 15), family history of prostate cancer (n = 682), and personal history of prostate problems (n = 17). After exclusions, 28,380 men were eligible for further analyses.

Table 1 presents the cohort characteristics by BMI category. The mean (SD) age of men was 62.3 (5.2) years. There was an inverse association between age and BMI (P < 0.001). The population was predominantly (89%) White. Mean (SD) and median BMI (interquartile range) were 27.6 (4.1) kg/m^2 and 27.0 (4.9) kg/m^2. Approximately half of all men were classified as overweight and 23.5% as obese or morbidly obese. A quarter of the

<table>
<thead>
<tr>
<th>BMI category</th>
<th>All Men</th>
<th>Normal (18.5-24.9 kg/m^2)</th>
<th>Overweight (25.0-29.9 kg/m^2)</th>
<th>Obese (30.0-34.9 kg/m^2)</th>
<th>Morbidly Obese (≥35.0 kg/m^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>28,380 (100)</td>
<td>7,370 (26.0)</td>
<td>14,331 (50.5)</td>
<td>5,224 (18.4)</td>
<td>1,455 (51.1)</td>
</tr>
<tr>
<td>Age (y; SD)</td>
<td>62.3 (5.2)</td>
<td>63.0 (5.5)</td>
<td>62.4 (5.2)</td>
<td>61.6 (5.0)</td>
<td>60.9 (4.8)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% White</td>
<td>89.4</td>
<td>86.5</td>
<td>90.3</td>
<td>91.0</td>
<td>90.7</td>
</tr>
<tr>
<td>% Black</td>
<td>3.6</td>
<td>3.5</td>
<td>3.2</td>
<td>4.4</td>
<td>5.6</td>
</tr>
<tr>
<td>% other</td>
<td>7.0</td>
<td>10.0</td>
<td>6.5</td>
<td>4.7</td>
<td>3.7</td>
</tr>
<tr>
<td>% with family history prostate cancer</td>
<td>7.5</td>
<td>8.0</td>
<td>7.3</td>
<td>7.5</td>
<td>5.84</td>
</tr>
<tr>
<td>% with personal history benign prostate problems</td>
<td>25.0</td>
<td>27.1</td>
<td>25.2</td>
<td>23.0</td>
<td>20.3</td>
</tr>
</tbody>
</table>

*p for ANOVA < 0.001.
1p for Chi^2 test for trend = 0.034.
^p for Chi^2 test for trend < 0.001.
participants had a personal history of benign prostate problems and a small proportion had a family history of prostate cancer (7.5%). Mean (SD) and median (interquartile range) baseline PSA concentrations were 1.48 (1.5) ng/mL and 1.05 (1.16) ng/mL, respectively.

**Plasma Volume, PSA Concentration, and PSA Mass According to BMI Category.** Table 2 shows the relationship between plasma volume, PSA concentration, PSA mass, and BMI. The mean PSA concentration decreased from 1.27 ng/mL in normal weight men to 1.07 ng/mL in morbidly obese men ($P < 0.001$). Estimated mean plasma volume increased with increasing BMI category, from 3.19 liters in normal weight men to 3.94 liters in morbidly obese men. Estimated PSA mass (PSA concentration × plasma volume), however, did not show a significant association with BMI ($P = 0.12$). Mean PSA mass values were 3.78, 3.95, 3.97, and 3.82 μg across the four BMI categories.

**Table 2. PSA concentration, plasma volume, and PSA mass according to BMI category**

<table>
<thead>
<tr>
<th>BMI category</th>
<th>Normal (18.5-24.9 kg/m²)</th>
<th>Overweight (25.0-29.9 kg/m²)</th>
<th>Obese (30.0-34.9 kg/m²)</th>
<th>Morbidly Obese (≥ 35.0 kg/m²)</th>
<th>$P$ for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>No men</td>
<td>7,328</td>
<td>14,331</td>
<td>5,223</td>
<td>1,454</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean PSA concentration* (ng/mL; 95% CI)</td>
<td>1.27 (1.25-1.29)</td>
<td>1.25 (1.23-1.26)</td>
<td>1.18 (1.16-1.20)</td>
<td>1.07 (1.03-1.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Plasma volume (liters)* (SD)</td>
<td>3.19 (0.08)</td>
<td>3.41 (0.08)</td>
<td>3.65 (0.08)</td>
<td>3.94 (0.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSA mass* (μg; 95% CI)</td>
<td>3.78 (3.72-3.85)</td>
<td>3.95 (3.90-4.00)</td>
<td>3.97 (3.89-4.05)</td>
<td>3.82 (3.67-3.97)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Adjusted for age, race, family history of prostate cancer, history of prostate problems, year of screen, and study center.

Discussion

We have confirmed in PLCO the widely reported inverse association between PSA levels and BMI (8, 9, 12, 13). The magnitude of the association, consistent with the findings of other studies, was not large, with mean PSA decreasing from 1.27 ng/mL in men with normal weight (BMI, 18.5-24.9 kg/m²) to 1.07 ng/mL in morbidly obese men ($P < 0.001$). Estimated mean plasma volume increased with increasing BMI category, from 3.19 liters in normal weight men to 3.94 liters in morbidly obese men. Estimated PSA mass (PSA concentration × plasma volume), however, did not show a significant association with BMI ($P = 0.12$). Mean PSA mass values were 3.78, 3.95, 3.97, and 3.82 μg across the four BMI categories.

Although prior papers have focused on hemodilution as being a function of BMI or obesity, the magnitude of a hemodilution effect would actually be determined not by BMI per se but by body size, specifically, body surface area (BSA), which is proportional to plasma volume in standard formulas. Although the two are highly correlated, $r = 0.7$ in the current cohort, the quantities are distinct; BMI divides weight by a power of height, whereas BSA multiplies weight by a power of height. Using a strict obesity criterion, the morbidly obese (BMI ≥ 35), who represent the top 5% of the PLCO population in terms of BMI, would be considered most at risk for a significantly lowered PSA concentration. However, if the effect is actually due to hemodilution, then those most at risk for a lowered concentration would be the top 5% of the population in terms of BSA. Based on PLCO data, only half of these latter men (those with BSA of ≥ 2.36 m²) would actually be morbidly obese; 40% would be obese (BMI, 30-35) and about another 10% overweight (BMI, 25-30). Conversely, among those who are morbidly obese, only about half would fall in the top 5% in terms of BSA. Thus, although there is considerable overlap in both groups, men with elevated BMI are not necessarily the most at risk for a hemodilution effect.

One alternative explanation for the decreased PSA concentration seen in obese men may be a decrease in circulating levels of androgens that are found in more obese men (8). Androgens play a major role in the growth and differentiation of the normal prostate (18). Furthermore, serum PSA levels in healthy men have been shown to be modulated by genetic variants of both PSA and androgen receptor genes (19). Therefore it is biologically plausible that serum PSA levels may be lower due to decreased levels of circulating testosterone in obese men. We do not have testosterone levels in all of the men in the cohort to test this hypothesis.
The main strengths of the current study are the large number of men (>28,000), the prospective nature of the screening, the fact that all PSA concentrations were measured in a single laboratory, the fact that the entire range of PSA values were used, and the fact that the men studied were unlikely to be harboring prostate cancer due to the 6-year cancer-free follow-up in all subjects. There are also limitations worthy of note. BMI was based on self-reported anthropometric information obtained during baseline screening of participants in the PLCO trial. Although not ideal, self-reported height and weight are commonly used and widely accepted as a valid and reliable alternative to technician measured anthropometry in epidemiologic studies (20). Additionally, we relied on estimated BSA to calculate plasma volume. Although the estimation formula is accepted in clinical practice and has been shown to correlate highly with measured plasma volume, the potential effect of using estimated plasma volumes on our results is unclear (21, 22). Lastly, African-American and other ethnic populations are underrepresented in this cohort. Previous studies have shown racial differences in PSA concentration (23, 24). The lack of minority subjects limits our ability to apply these findings to the general population.

Although the value of early detection of prostate cancer remains unknown, PSA screening is commonplace. This study has potential implications for PSA use and diagnosis of prostate cancer in large men. A hemodilution effect, if it exists, could alter the sensitivity and specificity of PSA in certain groups of men. Further research is necessary to show if this is in fact the case, and if so, to determine the magnitude of the effect in the population of men likely to be screened. In addition, the clinical utility and logistics of instituting different PSA cutoffs based on body size measurements must be carefully weighed.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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References

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