Obesity-Related Plasma Hemodilution and PSA Concentration Among Men With Prostate Cancer

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The prevalence of obesity in the United States has dramatically increased in the past decade. Increased body mass index (BMI) has been linked to death from colon, breast, and many other cancers. Although there are biological bases for increased risk of certain cancers in obese persons, delayed diagnosis may provide an explanation for advanced stage of disease and poor outcome. Obesity presents technical problems for cancer detection, since adiposity may hinder physical examination and interfere with imaging and ancillary tests. Likewise, obesity may negatively affect early diagnosis through assessment of serum concentrations of soluble tumor markers. For example, recent evidence suggests that prostate cancer screening may be adversely affected by increased BMI.

In the United States, most prostate cancer cases are diagnosed by needle biopsy of the prostate prompted by a high serum prostate-specific antigen (PSA) concentration. The ability to accurately detect prostate cancer can be compromised by any factor that decreases PSA concentration in the circulation. Multiple studies have found that obese men have lower PSA concentrations than nonobese men. Because men with higher body mass index (BMI) have greater circulating plasma volumes, lower PSA concentrations among obese men may be due to hemodilution.

Objective To determine the association between hemodilution and PSA concentration in obese men with prostate cancer.

Design, Setting, and Participants Retrospective study of men who underwent radical prostatectomy for prostate adenocarcinoma from 1988 to 2006, using data from the databases of the Shared Equal Access Regional Cancer Hospital (n=1373), Duke Prostate Center (n=1974), and Johns Hopkins Hospital (n=10 287). Multivariate linear regression models adjusting for clinicopathological characteristics were used to analyze the main outcome measures.

Main Outcome Measures Associations between BMI and mean adjusted PSA concentrations, mean plasma volume, and mean adjusted PSA mass (total circulating PSA protein, calculated as PSA concentration multiplied by plasma volume), assessed by determining P values for trend.

Results After controlling for clinicopathological characteristics, higher BMI was significantly associated with higher plasma volume (P<.001 for trend) and lower PSA concentrations (P=.02 for trend) in all cohorts. In 2 of the 3 cohorts, PSA mass did not change significantly with increasing BMI. In the third cohort, higher BMI was associated with increased PSA mass (P<.001 for trend), but only between BMI category less than 25 and the other categories.

Conclusions In men undergoing radical prostatectomy, higher BMI was associated with higher plasma volume; hemodilution may therefore be responsible for the lower serum PSA concentrations among obese men with prostate cancer. Prospective studies are needed to evaluate this association in screened populations.
OBESITY, PSA, AND PROSTATE CANCER

centrations than nonobese men.6-11 Since PSA concentration is regulated by androgens, investigators have hypothesized that lower PSA concentrations may result from decreased androgenic activity in obese men.5,12 However, men with higher BMI also have larger plasma volumes, which could decrease serum concentrations of soluble tumor markers—a phenomenon known as hemo-dilution.13

We hypothesized that the dilutional effects of higher plasma volume contributes to lower serum concentrations of tumor markers, which may lead to delayed cancer diagnosis among obese individuals. We tested this hypothesis in the context of prostate cancer and determined whether larger plasma volumes were associated with lower PSA concentrations among obese men with prostate cancer.

METHODS

Prior to analysis, institutional review board approval was obtained from each center for data collection and analysis. At all centers this was performed retrospectively, using a waiver of informed consent with the following 2 exceptions: at Augusta Veterans Affairs Medical Center, Augusta, Georgia, and at Duke University, Durham, North Carolina, data were collected retrospectively using a waiver of informed consent through November 2005 (Augusta) and March 2005 (Duke) and prospectively using written informed consent from each patient thereafter. Race was categorized as white, black, or other using patient-reported data. In all 3 cohorts, prostate weight was directly measured by the pathologist as the weight of the radical prostatectomy specimen.

Men who had received preoperative androgen-deprivation therapy, chemotherapy, or radiation therapy were excluded. Because men with lymph node–positive disease are at high risk for metastases, thus making it difficult to control for the contribution of distant disease to serum PSA concentration, we also excluded men with lymph node–positive disease. Because transurethral resection of the prostate affects prostate weight and serum PSA concentration, we further excluded men diagnosed through transurethral resection (clinical stage T1a/T1b).

Shared Equal Access Regional Cancer Hospital Cohort

We identified 2062 men who underwent radical prostatectomy for prostate adenocarcinoma from 1991 to 2006 at 5 medical centers contributing data to the Shared Equal Access Regional Cancer Hospital (SEARCH) database. SEARCH sites comprised the Veterans Affairs Medical Centers of Durham, North Carolina; Augusta, Georgia; and Greater Los Angeles, San Francisco, and Palo Alto, California. We excluded men who were missing data on BMI (n=455), preoperative PSA concentration (n=21), and prostate weight (n=167). We also excluded 20 men with lymph node–positive disease and 26 with clinical stage T1a/T1b, resulting in a study population of 1373.

Duke Cohort

We identified 4370 men in the Duke Prostate Center database who underwent radical prostatectomy for prostate adenocarcinoma from 1988 to 2006. We excluded men who were missing data on BMI (n=984), preoperative PSA concentration (n=387), and prostate weight (n=651). We also excluded 248 men with lymph node–positive disease and 126 with clinical stage T1a/T1b, resulting in a study population of 1374.

Johns Hopkins Cohort

We identified 12 661 men who underwent radical prostatectomy for prostate adenocarcinoma at the Brady Urological Institute at Johns Hopkins Hospital from 1988 to 2006. We excluded men who were missing data on BMI (n=1365), preoperative PSA concentration (n=116), prostate weight (n=102), and pathological Gleason sum (n=3). We also excluded 634 men with lymph node–positive disease and 154 with clinical stage T1a/T1b, resulting in a study population of 10 287.

Calculated Clinical Variables

Preoperative BMI was calculated as weight in kilograms divided by height in meters squared. Estimated body surface area was calculated as (body weight/height)0.72 × 0.007184.14 Estimated plasma volume (in liters) was calculated from body surface area as body surface area × 1.670.15 PSA concentration was measured as ng/mL. PSA mass (in micrograms), which denotes the total amount of PSA protein within the circulation at the time of determination of serum PSA concentration, was calculated as serum PSA concentration × total circulating plasma volume.

Statistical Analysis

All 3 cohorts were examined separately. The analysis used categories for BMI proposed by the World Health Organization, ie, less than 25.0 (normal), 25.0-29.9 (overweight), 30.0-34.9 (mildly obese), and 35.0 or greater (moderately to severely obese). Differences in the distribution of demographic and clinicopathological characteristics across BMI categories were compared using χ² test for categorical variables and analysis of variance for continuous variables.

We used multivariate linear regression to examine the association between BMI and 3 outcome variables: serum PSA concentration, plasma volume, and PSA mass. All analyses were mutually adjusted for potential confounding factors by including the following variables in the regression models: age at surgery (continuous); year of surgery (continuous); race (black, white, other); pathological prostate weight (continuous); and, in the case of the SEARCH database, surgical center (categorical). Because our goal was to study the relationship of BMI and PSA independent of any association between BMI and prostate cancer severity, and given that increased serum PSA values can also be due to more extensive prostate cancer, we also adjusted for cancer-specific variables by including the following variables in the regression models predicting PSA con-
centation and PSA mass: pathological Gleason score (2-6, 7, 8-10), extracapsular extension (absence vs presence), positive surgical margins (absence vs presence), and seminal vesicle invasion (absence vs presence).

Variables not exhibiting a normal distribution, such as serum PSA concentration, PSA mass, and prostate weight, were analyzed as continuous terms after logarithmic transformation. Body mass index was entered as a series of indicator variables for each BMI category. We tested for trend by entering the median BMI of each BMI category into the model as a continuous term and evaluating the coefficient by the Wald test. After determining relationships between BMI and log-transformed PSA concentrations and PSA mass for each BMI category using the linear regression model, values were back-transformed for proper interpretation of results. Associations with \( P < .05 \) were considered statistically significant. All statistical analyses were performed using STATA version 9.2 (StataCorp, College Station, Texas).

**RESULTS**

**BMI and Patient Characteristics**

Mean (SD) BMI was 28.1 (4.9) for the SEARCH, 28.1 (4.4) for the Duke, and 26.9 (3.3) for the Johns Hopkins cohorts. In the SEARCH cohort, 9% of patients were moderately to severely obese and an additional 21% were mildly obese, for a total obesity rate of 30% (Table 1). The rate of obesity was similar in the Duke cohort; however, it was lower in the Johns Hopkins cohort (16%). In all cohorts, patients with higher BMI were younger \( (P < .001) \), more likely to be treated in recent years \( (P < .001) \), and more likely to have a positive surgical margin \( (P = .01 \) for SEARCH; \( P < .001 \) for Duke and Johns Hopkins). Men with higher BMI had larger prostate weights; however, this association was statistically significant only in the Duke \( (P = .009) \) and Johns Hopkins \( (P < .001) \) cohorts.

**BMI, Plasma Volume, PSA Concentration, and PSA Mass**

Because BMI and plasma volume were both calculated as functions of height and weight, higher BMI was significantly associated with greater plasma volume \( (P < .001 \) for trend) in all study populations (Table 2). Men with a BMI of 35 or greater had 21% to 23% larger plasma volumes relative to normal-weight men. After adjusting for multiple clinicopathological variables, higher BMI was associated with lower preoperative PSA concentrations in the SEARCH \( (P = .001 \) for trend), Duke \( (P < .001 \) for trend), and Johns Hopkins \( (P = .02 \) for trend) cohorts (Table 2). Men with a BMI of 35 or greater had 11% to 21% lower PSA concentrations relative to normal-weight men.

We then examined the association between BMI and PSA mass, which reflects the total amount of PSA protein in circulation. After adjustment for various demographic and clinicopathological features, PSA mass did not change significantly with increasing BMI in the SEARCH \( (P = .76 \) for trend) or Duke \( (P = .50 \) for trend) cohorts (Table 2). In the Johns Hopkins cohort, PSA mass significantly increased with increasing BMI \( (P < .001 \) for trend) (Table 2). However, this was largely driven by lower PSA mass in normal-weight men: after exclusion of normal-weight men, there was no significant association between BMI and PSA mass \( (P = .13 \) for trend).

**COMMENT**

In this study of nearly 14,000 men with prostate cancer all treated by radical prostatectomy, we found that obese men had lower PSA values in all 3 cohorts studied. Moreover, we found that obese men had greater plasma volume in all cohorts. When calculating PSA

| Table 1. Demographic, Clinical, and Pathological Characteristics in Men Undergoing Radical Prostatectomy |
|----------------------------------|-------------------|-------------------|
| Characteristic                   | SEARCH (n = 1373) | Duke Prostate Center (n = 1974) | Johns Hopkins (n = 10287) |
| Age at surgery, mean (SD), y     | 61.1 (6.6)        | 62.5 (7.4)         | 57.8 (6.4)                 |
| Race, No. (%)                   |                   |                   |                             |
| White                            | 713 (52)          | 1652 (84)         | 9137 (91)                  |
| Black                            | 563 (41)          | 292 (15)          | 589 (6)                    |
| Other                            | 88 (6)            | 30 (2)            | 340 (3)                    |
| BMI, No. (%)                    |                   |                   |                             |
| <25.0                            | 357 (26)          | 452 (23)          | 2982 (29)                  |
| 25.0-29.9                       | 611 (44)          | 972 (49)          | 5661 (55)                  |
| 30.0-34.9                       | 285 (21)          | 416 (21)          | 1442 (14)                  |
| ≥35.0                           | 120 (9)           | 134 (7)           | 202 (2)                    |
| PSA, median (IQR), ng/mL        | 6.9 (4.9-10.2)    | 6.2 (4.4-9.3)     | 5.9 (4.3-8.6)              |
| Clinical stage, No. (%)         |                   |                   |                             |
| T1                               | 755 (57)          | 1426 (79)         | 6651 (65)                  |
| T2/T3                            | 567 (43)          | 382 (21)          | 3617 (35)                  |
| Pathological Gleason sum, No. (%)|                   |                   |                             |
| 2-6                              | 605 (44)          | 1556 (79)         | 6581 (64)                  |
| 7 (3 + 4, 4 + 3)                | 632 (46)          | 189 (10)          | 3189 (31)                  |
| 8-10                             | 136 (10)          | 218 (11)          | 517 (5)                    |
| Prostate weight, mean (SD), g    | 44.6 (22.8)       | 42.2 (19.7)       | 56.3 (20.8)                |
| Extracapsular extension, No. (%)| 309 (23)          | 538 (27)          | 3441 (13)                  |
| Positive surgical margins, No. (%)| 582 (43)          | 550 (28)          | 1323 (14)                  |
| Seminal vesicle invasion, No. (%)| 121 (9)           | 145 (7)           | 409 (4)                    |

Abbreviations: BMI, body mass index; IQR, interquartile range; PSA, prostate-specific antigen; SEARCH, Shared Equal Access Regional Cancer Hospital.

Values may not sum to the total study population for each database due to unavailability of data.

Calculated as weight in kilograms divided by height in meters squared.
mass (ie, the amount of PSA in the blood at the time of determination of PSA concentration, obese men in all 3 cohorts had similar or higher PSA mass. This suggests that hemodilution from larger plasma volume may be responsible for the lower PSA values observed among obese men with prostate cancer. These results need to be validated prospectively among men without prostate cancer.

Our findings agree with prior population-based studies suggesting that obese men have lower PSA concentrations than normal-weight men.6,7 In our study, after adjusting for clinicopathological disease characteristics, men in the most obese group had 11% to 21% lower serum PSA concentrations than normal-weight men, in line with the 10% to 32% decreased PSA concentration seen in population-based studies suggesting that greater leakage of PSA protein into the serum. While plausible, these explanations do not explain why this observation was observed only in the Johns Hopkins cohort. Regardless of the underlying cause, after controlling for hemodilution there was no significant decreasing trend for PSA mass observed in all 3 cohorts, suggesting that hemodilution may be responsible for the lower PSA concentrations in obese men.

Given that PSA is under androgenic control, an alternative explanation for the lower PSA concentrations is lower testosterone levels among obese men.5,18 If this is true, obese men would be expected to have lower PSA mass. However, in the current study, obese men had similar or higher PSA mass. Because obesity is associated with multiple changes in the hormonal milieu, particularly increased estrogen levels and decreased testosterone levels, it remains possible that tumor markers for other cancers such as endometrial and breast cancer, 19,20 which are controlled at the genetic level by sex steroid hormones, may be dually affected in obese individuals by both hemodilution and altered hormonal stimulation. Emerging markers for prostate cancer may be similarly affected. In the case of PSA, the current data suggest that hemodilution predominates and that hormonal effects are rendered negligible.

Furthermore, obesity-related hemodilution would occur only for tumor markers that are not systemically regulated. Whereas the concentrations of most hormones and serum proteins are tightly controlled by the body, molecular markers are produced by the tumor, leak into the serum at a steady rate, and are not regulated by the body. Therefore, changes in the volume of distribution will influence concentrations. Indeed, several small studies found that PSA concentrations increase acutely after dialysis.21,22

There is currently no level I evidence to suggest that PSA screening reduces prostate cancer mortality. Regardless, most of the US public

### Table 2. Plasma Volume, PSA Concentration, and PSA Mass by BMI Category

<table>
<thead>
<tr>
<th>BMI Category&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25.0</td>
</tr>
<tr>
<td><strong>Plasma volume, mean (SD), L</strong></td>
<td>SEARCH</td>
</tr>
<tr>
<td>Duke</td>
<td>3.18 (0.22)</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>3.22 (0.20)</td>
</tr>
<tr>
<td><strong>Adjusted PSA concentration, mean (SE), ng/mL&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>SEARCH</td>
</tr>
<tr>
<td>Duke</td>
<td>6.64 (0.23)</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>5.90 (0.07)</td>
</tr>
<tr>
<td><strong>Mean adjusted PSA mass, mean (SE), µg&lt;sup&gt;c&lt;/sup&gt;</strong></td>
<td>SEARCH</td>
</tr>
<tr>
<td>Duke</td>
<td>21.15 (0.70)</td>
</tr>
<tr>
<td>Johns Hopkins</td>
<td>19.02 (0.22)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI, body mass index; PSA, prostate-specific antigen; SEARCH, Shared Equal Access Research Cancer Hospital; Duke, Duke University Medical Center; Johns Hopkins, Johns Hopkins Medical Institutions.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup>Mean PSA concentration and mean PSA mass were adjusted for age, race, year of surgery, SEARCH site, prostate specimen weight, pathological Gleason sum, extracapsular extension, positive surgical margins, and seminal vesicle invasion.
believes that screening saves lives.\textsuperscript{33} Indeed, of all men older than 50 years, 75\% have had at least 1 PSA test and 57\% have had a PSA test within the past 12 months.\textsuperscript{24} Although our study did not address the risks and benefits of PSA-based prostate cancer screening, for men who do choose to be screened, lower PSA values among obese men may have clinical relevance. Lower PSA concentrations among obese men may result in fewer obese men having an elevated PSA value. Consequently, fewer obese men undergo prostate biopsy, leading to fewer cancers detected. Because cancer is generally a progressive process, some of these undetected cancers will continue to grow and may present at a later point, when they are larger and more difficult to treat. To what degree this may help explain the epidemiologic literature, in which obesity is associated with worse oncologic outcome among newly diagnosed men\textsuperscript{33,35,40} and with increased prostate cancer-specific mortality\textsuperscript{2}—but lower risk of diagnosis, at least in some subsets\textsuperscript{27-30}—remains to be determined.

Our analysis may be somewhat limited by restricting our population to men who underwent radical prostatectomy, a potential source of selection bias. Indeed, obese men are often discouraged from surgery due to concerns about surgical morbidity. Recent evidence also suggests that obesity presents technical challenges, which negatively affects the ability to completely resect the prostate\textsuperscript{31} and tumor.\textsuperscript{32} Regardless, in 2 of the 3 cohorts, the percentage of obese men closely paralleled national obesity prevalence rates.\textsuperscript{1} Moreover, it is essential that this phenomenon of plasma dilution first be confirmed in a surgically treated cohort so adjustment can be made for pathological parameters known to be associated with BMI, serum PSA concentration, or both, such as prostate weight\textsuperscript{9,6} and pathological Gleason score.\textsuperscript{33} Furthermore, the percentage decreases in PSA concentration noted among men with higher BMI in the current study of those who all had prostate cancer mirror the decreases reported in prior population-based studies.\textsuperscript{6,10}

Although estimation of plasma volume using body surface area is acceptable in clinical practice, other methods may provide more accurate estimates. For example, algorithms using lean body mass and hematocrit used for plasmapheresis may be arguably more ideal\textsuperscript{14}; however, lean body mass is not routinely measured in clinics or hospitals. With the increasing prevalence of obesity, recording of more detailed anthropometric measurements (body surface area, lean body mass, and total body fat) may be of future clinical relevance to better control for the potential dilutional effects of increased plasma volume on serum chemistry values and to provide more accurate prediction of drug distribution to ensure adequate therapy.

Despite these limitations, we believe our findings are valid, owing to the inclusion and adjustment for the major confounding variables affecting PSA concentration. Furthermore, the trends for mean adjusted PSA concentration, plasma volume, and mean adjusted PSA mass were very similar in 3 large databases from 2 distinct clinical settings (ie, tertiary care referral centers vs equal-access medical centers) varying in the proportion of blacks and with a total study population of nearly 14,000 men. This further strengthens the validity of our results, because the effect of race, which was previously shown by our group and others to influence serum PSA concentrations,\textsuperscript{33-37} was adequately controlled for in the analyses.

CONCLUSIONS

In 3 distinct prostate cancer cohorts, all treated by radical prostatectomy, hemodilution from increased plasma volume may be responsible for the observed decreased PSA concentration in men with higher BMI. This association needs to be confirmed prospectively in screened populations that include men without prostate cancer.

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REFERENCES


