Body Composition, Abdominal Fat Distribution, and Prostate-Specific Antigen Test Results

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Abstract

Background: There are competing theories explaining the observed inverse association between obesity and screening prostate-specific antigen (PSA) levels: (a) endocrine disturbances related to abdominal obesity influence PSA production and (b) increased plasma volume associated with obesity dilutes PSA. Under the endocrine disturbance hypothesis, fat mass, but not lean mass, and an abdominal distribution of fat are expected to be inversely associated with PSA levels. Under plasma volume dilution theory, PSA levels are inversely associated with both lean and fat mass and are independent of body fat distribution patterns.

Methods: Data on weight, percent body fat measured by bioimpedance, and waist circumference from ~8,000 men undergoing routine PSA screening were evaluated. Multivariate linear regression analyses controlling for age and race/ethnicity were used to determine whether fat, lean mass, or waist circumference were associated with PSA.

Results: PSA levels were significantly inversely associated with both lean and fat mass. In separate models, a 5-pound difference in lean mass and fat mass was associated, respectively, with a −0.9% (P < 0.001) and −0.7% (P = 0.001) difference in PSA test results. In a model that simultaneously considered lean and fat mass, a 5-pound difference in lean mass and fat mass was associated, respectively, with a −0.6% (P = 0.03) and −0.4% (P = 0.08) difference in PSA test results. Controlling for body mass index, a 1-inch difference in waist circumference was associated with a +0.9% (P = 0.01) difference in PSA levels.

Conclusion: The results are more consistent with predictions arising from the volume dilution theory than the hormone disturbance theory. (Cancer Epidemiol Biomarkers Prev 2009;18(1):331–6)

Introduction

The incidence of prostate cancer has significantly increased since the 1990s when widespread screening for prostate-specific antigen (PSA) began. Now, prostate cancer is the leading cancer diagnosed in men and the second leading cause of cancer mortality (1). The obesity epidemic has also recently been associated with prostate cancer mortality (2, 3). However, the evidence to support obesity as a cause for an overall increase in prostate cancer incidence has been mixed. Some studies have shown that obesity is associated with an increase in prostate cancer (4, 5), whereas others have shown that the two are not associated (6, 7). Several studies have shown that obese men have lower PSA levels at screening compared with nonobese men (8-11). There is a growing concern that obesity may reduce the sensitivity of PSA testing for detecting prostate cancer. Poorer screening sensitivity in the obese may explain the inverse association between obesity and prostate cancer incidence seen in some studies and the positive association between obesity and prostate cancer mortality (2, 3, 12).

It has been suggested that the association between obesity and lower PSA test values is due to obesity-related increases in plasma volume that effectively dilutes PSA levels (13, 14). We and others have developed physiologic models linking body size–related variability in plasma volume to PSA test results, and we have validated our volume dilution model in a sample of 10,000 men undergoing PSA screening (8, 9). This is a purely mechanical model in which the amount of circulating PSA protein (ng) is diluted in greater volumes of blood plasma in men with increasing body size to produce a lower PSA concentration (ng/mL) at PSA screening. However, a competing hypothesis is that obesity leads to an endocrine disturbance characterized by decreases in androgen levels and increases in estrogen levels, which in turn lead to lower PSA production. Studies have shown adipose tissue to be a metabolically active organ (15, 16). Obesity has been found to be significantly associated with lower testosterone levels, and abdominal adipose tissue in particular has been shown to decrease androgen production (17-23). Additionally, obesity is associated with increased peripheral aromatization of androstenedione to estrone, and in men, obesity is associated with higher levels of estrogen (24-30). However, the evidence linking circulating androgens to circulating PSA levels is scant. Some studies have shown PSA production to be under androgenic control (31) or associated with testosterone (32-34), although other studies have found no association at all (35, 36).
These two competing hypotheses would lead to starkly different predictions about how lean mass, fat mass, and body fat distribution would be associated with PSA. Under a volume dilution model, both lean and fat mass would be inversely associated with PSA, and because both lean and fat tissue require adequate blood supply, interindividual variation in both lean and fat mass would be associated with interindividual variation in plasma volume. Conversely, under the endocrine disturbance hypothesis, because increased fat mass causes the endocrine disturbances, only fat mass would be predicted to be inversely associated with PSA test scores (37, 38). Furthermore, under a paradigm focusing on endocrine-based effects, because testosterone is required to build lean mass and PSA production is under androgenic control, lean mass is expected to be positively associated with PSA levels (39, 40). Under a volume dilution model, interindividual variation in fat distribution across the body would not be associated with interindividual variation in PSA test scores; only the total volume is relevant, not the distribution of volume. Conversely, under an endocrine disturbance model, increased abdominal fat mass should be inversely associated with PSA test scores because abdominal fat is more hormonally active than fat in other places on the body (41, 42).

Using PSA test scores, body composition, and waist circumference data from a large cross-sectional data set, we set out to test the accuracy of the predictions arising from these competing hypotheses.

Materials and Methods

EHE International, Inc. (EHE) provides annual routine screening physical exams to individuals employed at corporations who offer EHE services as part of the corporate wellness plan. The exams are offered to the employees of participating companies free of charge to the employee. Companies differ in their policies about which levels of employees are eligible for the physical exam, but many companies offer it to all levels of employees and their spouses. The physical exams take place at six EHE-owned centers (New York City, NY, Stamford, CT, Morristown, NJ, Houston, TX, Chicago, IL, and Boston, MA) and at a network of over 60 physician offices across the country. The network offices meet EHE quality control standards for the exam procedures and submit blood samples to the same central clinical laboratory used by EHE-owned centers. All exam data are recorded electronically in a centralized medical record system maintained by EHE and laboratory results are electronically submitted by the laboratory.

Height and weight were measured using rigid stadiometers and digital clinical scales at EHE centers and physician offices in the network. Clinical scales are calibrated daily. Percent body fat was measured via bioimpedance using Tanita clinical scales (model TPF 300). Waist circumference was measured using a flexible, nonstretching, cloth tape by an EHE clinical staff member who identified the waist by palpating the iliac crest. The tape was wrapped around midaxillary line, parallel to the floor, and the measurement was taken during normal respiration. Blood serum samples taken during the exams and overnight were delivered to a commercial clinical laboratory, LabCorp, Inc. Serum PSA levels were measured using a immunochromiluminometric assay (LabCorp protocol 010322), which has a listed detection limit of 0.1 ng/mL, although past research shows that the limit is lower than this (43). In the overall study population with percent body fat or waist circumference data, only three men had PSA values below 0.1 ng/mL.

Statistical Analyses. Data can be retrieved from the centralized digital medical record system and stripped of identifiers before being compiled into an ASCII text file that can be read by standard statistical programs. Data were retrieved in this manner on body mass index (BMI), percent body fat, waist circumference, PSA levels, and demographic characteristics for all men having PSA tests between January 1, 2004 and June 30, 2006. The Columbia Presbyterian Medical Center Institutional Review Board approved the study protocol and designated it as nonhuman research involving deidentified records previously collected for other purposes. EHE provides routine annual screening PSA tests to men 40 y and older, although younger men can request that PSA tests be done. Cross-sectional linear regression analyses of predictors of PSA levels were conducted using PSA data from the first or only exam the men participated in during the period under review. Analyses were conducted using Statistical Analysis System V9.1 (SAS, Institute, Inc.). The PSA data were analyzed for all values greater than zero. PSA data were log e transformed to provide a more normal data distribution. Statistical analyses were done on data from men 40 y and older, the population for which routine PSA testing is done. Analyses were also confined to men with a BMI of >16 because values below this are likely to represent data entry errors or the presence of underlying disease processes. Of the 10,796 men meeting these two criteria, body composition data were available from 8,028 men and waist circumference data were available from 8,538 men.

Lean and fat mass were calculated from the data on body mass and percent body fat (44). In a two-compartment model, water is included in lean mass, but the volume dilution theory postulates that PSA is diluted by increased blood plasma volume associated with higher lean mass and fat mass. Therefore, associations between lean mass and PSA levels may be influenced by the mass attributable to blood plasma. To investigate this possibility, blood plasma volume was calculated for each man and multiplied by the density of blood plasma (1.02 g/mL) to estimate the mass attributable to blood plasma (8). Analyses of the association between lean mass and PSA were repeated with estimated blood plasma mass subtracted from the lean mass measure.

Multivariate linear regression analyses were used to determine whether fat mass, lean body mass, or waist circumference was associated with PSA. PSA levels were natural log transformed to generate a more normal data distribution and results are expressed as the percent difference in PSA associated with a 5-pound difference in lean or fat mass and 1-inch difference in waist circumference. Deviations from linearity were assessed by including squared functions of lean and fat mass and waist circumference in the model. Analyses controlled for age as a continuous variable and self-reported race, coded using a series of indicator variables as Asian,
A direct measure of body fat distribution was not available in the data, and so waist circumference controlling for BMI and/or fat mass was used as a surrogate measure of an abdominal distribution of body fat. When waist circumference and BMI were included in the same statistical model, interindividual differences in waist circumference are interpreted as differences in the distribution of fat in the abdominal region for a constant BMI.

Results

Data on body composition were available from 8,026 men, whereas data on waist circumference were available from 8,538 men. Table 1 provides data on demographic characteristics, PSA levels, BMI, fat mass, lean mass, and waist circumference for these men. Demographic and clinical characteristics of those with and without body composition measures did not vary. Lean and fat mass were correlated (0.54, \( P < 0.001 \)), and lean mass and fat mass were correlated with waist circumference (0.58, \( P < 0.001 \); and 0.88, \( P < 0.001 \), respectively).

Overall PSA test results were low in this relatively young population. When analyzed in separate models, lean mass and fat mass were both significantly inversely associated with PSA test results. However, in a single model that included variables for both fat and lean mass, the inverse association between PSA test results and fat mass was of only borderline statistical significance. Table 2 shows the percent difference PSA values associated with a 5-pound difference in lean and fat mass. When the analyses were repeated with estimated blood plasma mass subtracted from lean mass, the associations between lean mass and PSA levels were identical to those observed in the initial analyses of total lean mass (results not shown).

Table 3 presents results from several regression models assessing associations between waist circumference and PSA levels. When considered alone, and serving as a proxy for overall body size, waist circumference was significantly inversely associated with PSA test results. Further analyses controlled for BMI, fat mass, and BMI and fat mass, so that waist circumference could be interpreted as a measure of an abdominal distribution of body fat. In these analyses, for a given BMI or fat mass, each inch increase in waist circumference is interpreted as representing a higher concentration of body fat in the abdominal region. After control for BMI or fat mass, waist circumference was positively associated with PSA levels with borderline significance. After control for both BMI and fat mass, waist circumference was significantly positively associated with PSA levels.

Discussion

Two competing theories explaining the association between obesity and lower PSA screening test results have been suggested: (a) that obesity is related to increases in blood plasma volumes that effectively dilute out PSA and (b) that obesity is related to disturbances in

<table>
<thead>
<tr>
<th>Table 2. Association between lean mass, fat mass, and screening PSA level</th>
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<tbody>
<tr>
<td>Percent difference in PSA* (( P ))</td>
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<tr>
<td>5-lb difference in lean mass</td>
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<tr>
<td>5-lb difference in fat mass</td>
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* Controlling for age and race/ethnicity with only lean mass in model.
† Controlling for age and race/ethnicity with only fat mass in model.
‡ Controlling for age and race/ethnicity with both lean and fat mass in model.
the androgen and estrogen levels that alter PSA production. These two competing theories produce starkly different predictions for how lean and fat mass and body fat distribution are associated with PSA levels. The hormone disturbance theory posits that the aromatization of peripheral fat tissue, particularly abdominal fat, produces estrogen and lowers androgen levels, which in turn reduces PSA production. The volume dilution theory posits that interindividual variability in all bodily compartments requiring a blood supply would cause interindividual variability in plasma volume and affect PSA test results and that test results would be independent of the distribution of body fat.

The results presented here argue against the hormonal disturbance theory being correct; predictions based on the hormonal disturbance theory were not fulfilled in the data (see Table 4). In fact, the analyses show that higher lean mass is more strongly, inversely, associated with PSA than higher fat mass, a direct contradiction of the predictions arising from the hormone disturbance theory. The stronger inverse association with lean mass as opposed to fat mass is consistent with lean mass being more metabolically active than fat mass (45, 46) and perhaps requiring a greater blood supply per unit mass than fat tissue.

In the analyses of waist circumference in which BMI and/or fat mass was controlled for as a covariate, interindividual variation in waist circumference is interpreted as a measure of differences in abdominal fat. For a given BMI, a higher waist circumference indicates a greater distribution of body fat in the abdominal region. In men, obesity, and particularly abdominal obesity, is associated with lower androgen levels and higher estradiol levels (21, 22, 27-29). In women, central obesity is also associated with a higher risk for hormonally related cancers such as breast and endometrial cancers (47-50). Thus, if the hormonal disturbance theory is correct, increasing abdominal fat distribution should be associated with lower PSA levels. However, contrary to these predictions, after control for BMI and fat mass, waist circumference was positively associated with PSA test results. The observed positive association is not completely congruent with predictions arising from the volume dilution hypothesis. The prediction was that, because adipose tissue anywhere on the body requires additional blood volume and it is this phenomenon that drives the association between BMI and PSA test results, a particularly abdominal distribution of adipose tissue would not be associated with PSA test results. Because statistically it is not possible to prove a null hypothesis, analyses of waist circumference controlling for BMI and/or fat mass were a logically weak test of the volume dilution theory. However, these analyses were a logically strong test of the hormonal disturbance theory–based prediction of an inverse association and the observations were directly contrary to the prediction.

Although numerous articles have reported on inverse associations between BMI and PSA levels, to our knowledge associations between PSA levels and lean and fat mass and abdominal body fat distribution have not been directly assessed previously (8-11). In a recent study of Japanese men, Ando and colleagues (51) observed that PSA levels were inversely associated with percent body fat, but they did not assess associations with estimated fat mass. Analyses of NHANES data showed that PSA levels were inversely associated with total body water, which is consistent with an underlying volume dilution theory (11). However, PSA levels were not associated with triceps or subscapular skin folds, indirect measures of total adiposity, and were not associated with waist circumference (11).

The analyses presented here do not consider several other factors that might cause interindividual variation in PSA levels, such as interindividual differences in the transcription of the PSA gene, polymorphisms in the gene, and variation in prostate size that may also be influenced by obesity. Furthermore, it does not consider the kinetics through which PSA leaks into circulation. However, past work showing, across different populations, that BMI is inversely associated with PSA test

<table>
<thead>
<tr>
<th>Predicted association with PSA test score</th>
<th>Observed association</th>
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<tbody>
<tr>
<td>Volume dilution theory</td>
<td>Hormonal disturbance theory</td>
</tr>
<tr>
<td>Lean mass</td>
<td>Negative association</td>
</tr>
<tr>
<td>Fat mass</td>
<td>Positive association</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>Negative association</td>
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Table 4. Theory-based predictions for associations between PSA test scores, fat mass, lean mass, and abdominal obesity and observed associations

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**Table 3. Association between waist circumference and screening PSA level**

<table>
<thead>
<tr>
<th></th>
<th>Model 1*</th>
<th>Model 2†</th>
<th>Model 3‡</th>
<th>Model 4§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent difference in PSA* (P)</td>
<td>−0.5% (0.001)</td>
<td>0.9% (0.01)</td>
<td>0.8% (0.05)</td>
<td>1.2% (0.002)</td>
</tr>
</tbody>
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*Controlling for age and race/ethnicity.
†Controlling for age, race/ethnicity, and BMI.
‡Controlling for age, race/ethnicity, and fat mass.
§Controlling for age, race/ethnicity, BMI, and fat mass.
results has not considered such factors either (8-11). The results presented here compare β coefficients for the association between lean mass and PSA and for the association between fat mass and PSA to a priori expectations derived from two competing theories. For unmeasured factors to cause spurious associations, one must expect that unmeasured factors to cause spurious associations or affect one β coefficient but not the other, the unmeasured variable would have to be associated with PSA and differentially associated with lean and fat mass. At worst, we expect that unmeasured determinants of variation in PSA levels will cause a bias to the null.

The Tanita scales use a two-compartment model of the body to estimate percent body fat and represent a clinical rather than gold standard measure of body composition, which four-compartment models provide. However, the Tanita devices have been validated in cross-sectional studies against gold standard four-compartment models (52) and against reference measures of body composition, including dual-energy X-ray absorptiometry (53-55) and underwater weighing (56). In addition, they have been validated against four-compartment models, dual-energy X-ray absorptiometry, and underwater weighing in prospective studies of weight loss and ability to detect the modest changes in body fat observed in these studies (57-60). Across its clinical sites, EHE uses a standardized protocol, which requires no food consumption in the 8 hours before the physical exam. There is the possibility that extremes of hydration status can affect bioimpedance results, although variation within the reference range has relatively little effect on percent body fat estimates (61-63). Our data for percent body fat are very similar to those obtained from a nationally representative sample of men from the NHANES III study. Because 80% of our study population was composed of non-Hispanic white males, data from this component of our study population were compared with data from the non-Hispanic, white male NHANES III population. In our study population, the average percent body fat for non-Hispanic white males aged 40 to 49.9 years (n = 3,510) was 23.7 (SD, 6.2), among men aged 50 to 59.9 years (n = 2,314) was 25.3 (SD, 6.2), and among men aged 60 to 69.9 years (n = 512) was 25.6 (SD, 5.8). In NHANES III, the average percent body fat for non-Hispanic white males aged 40 to 49.9 years was 24.2 (SD, 5.7), for men aged 50 to 59.9 years was 25.1 (SD, 6.0), and for men aged 60 to 69.9 years was 26.2 (SD, 5.5) (64).

We and others have independently developed mathematical/physiologic models relating differences in body size to differences in blood plasma volumes to explain the association between obesity and lower PSA test results (8, 9). We have previously validated our model in the population studied in this current report and have used it to estimate PSA test results in obese (3.5 ng/mL) and morbidly obese (3.1 ng/mL) individuals that are equivalent to a result of 4.0 (ng/mL) in normal weight and overweight men (9). The results presented here provide further evidence that the association between obesity and lower PSA test results is due to a dilution effect and provide support for our physiologic model.

Disclosure of Potential Conflicts of Interest

A. Rundle: serves on the Medical Advisory Board of EHE; A.I. Neugut: serves on the Medical Advisory Board of EHE. EHE did not play a role in the design of the study, analyses of the data, interpretation of the data, in the decision to submit the manuscript for publication, or in the writing of the manuscript. EHE did verify that the text in Materials and Methods describing the company and its programs was factually correct.

Acknowledgments

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