Racial Differences in Adipose Tissue Distribution and Risk of Aggressive Prostate Cancer among Men Undergoing Radiotherapy

Emma H. Allott1,2,3, Lauren E. Howard3,4, Hai-Jun Song5,6, Katharine N. Sourbeer1,3, Bridget F. Koontz5, Joseph K. Salama5,6, and Stephen J. Freedland1,3,7

Abstract

Background: Although elevated body mass index (BMI) has been associated with increased risk of aggressive prostate cancer, the importance of adipose tissue distribution is not well understood. We examined associations between overall and visceral obesity and aggressive prostate cancer risk. Moreover, given racial differences in adipose tissue distribution, we examined whether race modified these associations.

Methods: We conducted a cross-sectional analysis of 308 radiotherapy-treated patients with prostate cancer within the Durham VA from 2005 to 2011. Multivariable logistic regression examined the association between BMI categories and tertiles of waist circumference (WC), visceral fat area (VFA), and periprostatic adipose tissue area (PPAT) with high-grade prostate cancer risk (Gleason score ≥7 vs. ≤6). Models stratified by race examined whether these associations differed between black and nonblack men.

Results: Both elevated BMI (P\text{trend} = 0.054) and WC (P\text{trend} = 0.040) were associated with increased high-grade prostate cancer risk, with similar results between races, although the association with BMI was not statistically significant. In contrast, elevated VFA was associated with increased aggressive prostate cancer risk in black men (P\text{trend} = 0.002) but not nonblack men (P\text{trend} = 0.831), with a significant interaction between race and VFA (P\text{interaction} = 0.035). Though similar patterns were observed for PPAT, none was statistically significant.

Conclusions: Among men undergoing radiotherapy for prostate cancer, visceral obesity is associated with increased aggressive prostate cancer risk, particularly among black men. If confirmed in future studies, these results suggest that adipose tissue distribution differences may contribute to prostate cancer racial disparity.

Impact: These findings highlight the need to elucidate mechanisms contributing to racial differences in the association between visceral obesity and aggressive prostate cancer. Cancer Epidemiol Biomarkers Prev; 23(11); 2404–12. ©2014 AACR.

Introduction

In the United States, prostate cancer is the most frequently diagnosed cancer among men, and the second most common cause of cancer deaths (1). Black men have 1.6-fold higher prostate cancer incidence and 2.5-fold higher prostate cancer mortality, relative to white men (1). Although socioeconomic factors certainly contribute to this health disparity, there is evidence that race-specific differences in tumor biology play an important role (2, 3).

Multiple meta-analyses have identified overall obesity, defined as body mass index (BMI) ≥30 kg/m², to be a risk factor for aggressive prostate cancer (4). Although the prevalence of overall obesity among men in the United States does not differ by race (5), there are established differences in adipose tissue distribution between black and nonblack men (6, 7). Relative to white men, black men have less visceral adipose tissue, a depot which is known to play an important role in obesity-mediated metabolic changes and inflammation (4, 8). Although visceral obesity has been associated with increased risk of aggressive prostate cancer in both white (9) and black men (10), no studies to our knowledge have examined whether the strength of the association between visceral obesity and aggressive prostate cancer differs between races. Furthermore, although one study has reported an association between increased periprostatic adipose tissue area (PPAT) and elevated risk of aggressive prostate cancer.
cancer in white men (11), none have examined whether there are racial differences in PPAT quantity and whether elevated PPAT is associated with increased risk of aggressive prostate cancer in black men.

The objective of this study was to examine the association between obesity, adipose tissue distribution, and risk of aggressive prostate cancer using a cross-sectional analysis of black and nonblack men who received radiotherapy for biopsy-confirmed prostate cancer. We hypothesized that visceral obesity would be associated with increased risk of aggressive prostate cancer and that racial differences in adipose tissue distribution would modify this association. Specifically, we hypothesized that there would be a stronger association between visceral obesity and increased risk of aggressive prostate cancer in black men, given the higher prevalence of obesity-associated comorbidities in this racial group (12, 13).

Materials and Methods

Study population and design

After obtaining Institutional Review Board approval, we identified all men (n = 521) with biopsy-confirmed prostate cancer who were treated with definitive external beam radiotherapy (XRT) or brachytherapy at the Durham Veterans Affairs (VA) Medical Center between 2005 and 2011. The population used for this study was selected because of the availability of pretreatment pelvic and abdominal CT scans for radiotherapy planning, enabling accurate quantification of various adipose tissue depots, as described below. Thus, we excluded men with missing pelvic (n = 109) or abdominal CT scans (n = 80). In addition, we excluded men with missing data for BMI (n = 8), PSA (n = 7), clinical stage (n = 7), and biopsy Gleason score (n = 2), giving rise to a final population of 308 patients.

Adipose tissue measurement

Visceral fat area (VFA), subcutaneous fat area (SFA), and PPAT were quantified from radiotherapy planning CT scans using Eclipse software (Varian Medical Systems) by a single investigator blinded to demographic and clinical characteristics (EHA).

PPAT was measured using a single CT slice at the level of the first point of the pubic symphysis (14). Briefly, the Eclipse freehand drawing tool was used to contour a region extending from the posterior pubic bone, along the lateral border of obturatorius internus muscle and anterior gluteus maximus muscle to the anterior coccyx bone (Fig. 1). Pelvis size was defined as the total area of this contoured region, and PPAT was defined as the total area of adipose tissue within this region. We differentiated between adipose tissue and other tissues using thresholding by Hounsfield Units (HU), with adipose tissue defined as −190 to −30 HU. This method effectively excluded the prostate.

Figure 1. Calculation of PPAT area and PPAT density measurements from a single CT slice at the level of the first point of the pubic symphysis (A) and calculation of VFA, SFA, and WC from a single CT slice at the level of L4/L5 (B).
rectum, and mesorectum. PPAT density ratio was calculated as PPAT divided by pelvis size.

VFA and SFA were calculated using the Eclipse automatic area tool on a single CT slice at the level of L4/L5, as previously described (ref. 15; Fig. 1). Because waist circumference (WC) was not measured among these patients in clinic, we determined it retrospectively from the same CT slice as for VFA and SFA. Measurement of WC from a CT scan with the patient in a supine position has previously been demonstrated to correlate well with WC measured using a tape measure with the patient standing, with intraclass correlation coefficients between 0.97 and 0.98 (16–18). Body outline was traced using the Eclipse freehand drawing tool and WC was calculated using ImageJ (rsbweb.nih.gov/ij/). Finally, volume of prostate was calculated automatically using the Eclipse volume of interest tool using the contours entered by the treating physician at the time of radiotherapy (Fig. 1).

Obesity definitions
Height and weight measured at the closest time before radiotherapy were abstracted from patient charts. Patients were then stratified into four BMI categories according to World Health Organization definitions; normal weight (BMI < 25 kg/m²), overweight (BMI ≥ 25 kg/m² and <30 kg/m²), obese (BMI ≥ 30 kg/m² and <35 kg/m²), and severely obese (BMI ≥ 35 kg/m²). Given that no clearly defined categories exist for VFA, SFA, WC, or PPAT, these measures of obesity were divided into tertiles based on the entire cohort. In secondary analysis, race-specific VFA and PPAT tertiles were generated among black and nonblack men.

Statistical analysis
Differences in demographic, clinical, and anthropometric features between black (n = 193) and nonblack (n = 115) men were examined using t tests for normally distributed continuous variables, Wilcoxon rank-sum tests for non-normally distributed continuous variables, and χ² tests for categorical variables. Nonblack men were either white (n = 111) or nonblack non-white (n = 4). Correlation coefficients between measures of obesity (BMI, WC, SFA, VFA, and PPAT), all treated as continuous variables, and between each measure of obesity and duration of preradiotherapy androgen deprivation therapy (ADT) were calculated using Spearman correlation.

Multivariable logistic regression analysis was used to investigate the association between obesity (categories of BMI, WC, SFA, VFA, and PPAT; each assessed individually) and risk of aggressive prostate cancer, as defined by biopsy Gleason score ≥7 versus ≤6, using the lowest category of each obesity measure as the reference group. This standard definition of aggressive prostate cancer was selected to enable comparison of these results with prior studies using this definition (9, 10, 19–22). When the three noncollinear adiposity measures (i.e., SFA, VFA, and PPAT) were all added to the same multivariable model, the results did not substantially change relative to the multivariable model with each adiposity measure assessed individually. Thus, only models with each adiposity measure assessed individually are shown. Models were adjusted for age at radiotherapy (continuous), race (black vs. nonblack), pretreatment PSA (continuous, log-transformed), clinical stage (T1 vs. T2/T3), duration of preradiotherapy ADT [none, <median (2.47 months), ≥median], and year of radiotherapy (continuous). We did not have access to diabetes status or family history of prostate cancer in this study. We tested for trends across increasing obesity categories using multivariable logistic regression analysis of obesity category medians. Models were stratified by race to examine whether the association of obesity categories with biopsy Gleason score differed between black and nonblack men. We also tested for interaction between obesity categories and race by incorporating a product term into our models. Furthermore, we repeated our analysis using race-specific tertiles for VFA and PPAT. Finally, in exploratory analysis, we repeated our analysis among men who never received ADT (n = 154) before radiotherapy.

All statistical analyses were carried out in Stata version 11.0 (Stata Corp.). Differences were considered to be statistically significant at P < 0.05.

Results
Baseline characteristics by race
Black men were younger at the time of radiotherapy (63.4 vs. 65.4 years old; P = 0.009) and more recently treated (P = 0.025) relative to nonblack men (Table 1). In addition, black men had lower clinical stage compared with nonblack men (P = 0.001), and were significantly less likely to have received ADT before radiotherapy (P = 0.013). However, among men who did receive ADT before radiation (50% of our total cohort), there was no difference in duration of ADT by race (P = 0.183). Given that ADT can promote weight gain (23), we examined whether duration of preradiotherapy ADT was correlated with measures of obesity which were obtained at the time of radiotherapy (i.e., after neoadjuvant ADT). We found that, among men who received ADT, longer duration of ADT before radiation was not associated with any obesity measure (data not shown).

There were no differences in surrogate measures of obesity, BMI (29.6 vs. 28.6 kg/m²; P = 0.698), or WC (104.3 vs. 104.9 cm; P = 0.264), between black and nonblack men (Table 2). Neither was there any significant difference in amount of subcutaneous adipose tissue between races, directly measured using SFA (296.1 vs. 289.5 cm²; P = 0.349). However, black men had significantly less visceral adipose tissue (VFA; 190.3 vs. 245.8 cm²; P < 0.0001) and significantly less PPAT (35.5 vs. 41.2 cm²; P = 0.0001), relative to nonblack men. Black men also had smaller pelvis size relative to nonblack men (P = 0.001); however, PPAT area remained significantly lower among black men even after adjusting for pelvis size (PPAT density ratio; P = 0.002; Table 2). Among all men, all measures of obesity correlated with each other, with...
similar correlation coefficients in black and nonblack men after stratifying by race (Table 3).

**Association between surrogate measures of obesity and risk of aggressive prostate cancer does not differ by race**

In this population of radiotherapy-treated patients with prostate cancer, severely obese men (BMI $\geq 35$ kg/m$^2$) were nearly 3-fold more likely to have aggressive prostate cancer, relative to normal weight men [BMI $< 25$ kg/m$^2$; odds ratio (OR) 2.97; 95% confidence interval (CI), 1.21–7.26; Table 4]. When we restricted our analysis to black men, severe obesity remained significantly associated with approximately 3-fold increased risk of elevated biopsy Gleason score (OR 3.71; 95% CI, 1.14–12.1). Although the direction and magnitude of this association were similar for nonblack men, it did not reach statistical significance (OR 2.54; 95% CI, 0.59–10.91). Similarly, larger WC, a commonly used surrogate of visceral obesity, was associated with significantly increased risk of aggressive prostate cancer among our entire cohort of radiotherapy-treated patients (3rd tertile vs. 1st tertile; OR 2.0; 95% CI, 1.02–3.92; $P_{\text{trend}} = 0.04$) and among black men only (3rd tertile vs. 1st tertile; OR 2.45; 95% CI, 1.04–5.77; $P_{\text{trend}} = 0.04$) with a similar direction, but lower magnitude association generating a nonsignificant trend among...
Association between visceral obesity and risk of aggressive prostate cancer is modified by race

Although the associations between surrogate measures of obesity (i.e., BMI and WC) and aggressive prostate cancer risk were similar in black and nonblack men, stratification by race revealed contrasting associations between VFA, a direct measure of visceral obesity, and aggressive prostate cancer risk. Specifically, although higher VFA was significantly associated with increased risk of aggressive prostate cancer among black men (3rd tertile vs. 1st tertile; OR 4.71; \( P < 0.0001 \)), this association was absent in nonblack men. These findings suggest that the association between visceral obesity and risk of aggressive prostate cancer risk are significantly contrasting by race, while similar trends were observed between PPAT area and risk of aggressive prostate cancer in black and nonblack men (data not shown).

Discussion

In this cross-sectional, hypothesis-generating study of radiotherapy-treated patients with prostate cancer, surrogate measures of overall and visceral obesity, BMI and WC, respectively, were associated with increased risk of high-grade prostate cancer in both black and nonblack men. In contrast, the association between elevated VFA, a direct measure of visceral obesity, and increased risk of high-grade prostate cancer was modified by race with a significant positive association in black men which was absent in nonblack men. These findings suggest that although surrogate measures of obesity are appropriate for studying the association between obesity and prostate cancer aggressiveness in both black and nonblack men, a more precise measure of visceral adiposity reveals significantly contrasting associations by race and may provide

Table 3. Correlation between adipose tissue measurements

<table>
<thead>
<tr>
<th></th>
<th>BMI (kg/m²)</th>
<th>WC (cm)</th>
<th>SFA (cm²)</th>
<th>VFA (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.91, ( P &lt; 0.0001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.91, ( P &lt; 0.0001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.91, ( P &lt; 0.0001 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SFA (cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.88, ( P &lt; 0.0001 )</td>
<td>0.92, ( P &lt; 0.0001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.88, ( P &lt; 0.0001 )</td>
<td>0.90, ( P &lt; 0.0001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.88, ( P &lt; 0.0001 )</td>
<td>0.94, ( P &lt; 0.0001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VFA (cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.65, ( P &lt; 0.0001 )</td>
<td>0.77, ( P &lt; 0.0001 )</td>
<td>0.56, ( P &lt; 0.0001 )</td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.70, ( P &lt; 0.0001 )</td>
<td>0.82, ( P &lt; 0.0001 )</td>
<td>0.50, ( P &lt; 0.0001 )</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.67, ( P &lt; 0.0001 )</td>
<td>0.77, ( P &lt; 0.0001 )</td>
<td>0.60, ( P &lt; 0.0001 )</td>
<td></td>
</tr>
<tr>
<td>PPAT (cm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.24, ( P &lt; 0.0001 )</td>
<td>0.31, ( P &lt; 0.0001 )</td>
<td>0.25, ( P &lt; 0.0001 )</td>
<td>0.41, ( P &lt; 0.0001 )</td>
</tr>
<tr>
<td>Nonblack</td>
<td>0.21, ( P = 0.024 )</td>
<td>0.30, ( P = 0.001 )</td>
<td>0.20, ( P = 0.036 )</td>
<td>0.35, ( P = 0.0001 )</td>
</tr>
<tr>
<td>Black</td>
<td>0.28, ( P = 0.0001 )</td>
<td>0.33, ( P &lt; 0.0001 )</td>
<td>0.31, ( P &lt; 0.0001 )</td>
<td>0.39, ( P &lt; 0.0001 )</td>
</tr>
</tbody>
</table>

NOTE: Correlation coefficients calculated using Spearman rank test.
some mechanistic insight into the racial disparity in prostate cancer. Although it is known that obesity is associated with increased risk of aggressive, but not total prostate cancer (4), few studies have examined whether the association between obesity and risk of aggressive prostate cancer differs by race. One study reported that race modified the association between obesity and elevated risk of prostate cancer recurrence, with a significant association in black men but not in nonblack men (22). Other studies have noted a higher prevalence of obesity among black men in their cohorts, potentially contributing to the higher frequency of aggressive disease in this racial group (19, 20). On the contrary, two studies reported obesity to be a risk factor for aggressive prostate cancer regardless of race (24, 25). Thus, our finding adds to the literature that overall obesity is associated with increased risk of aggressive prostate cancer in both black and nonblack men. In keeping with the lack of association between overall obesity and risk of total prostate cancer (4), a large meta-analysis reported a null association between visceral obesity, predominantly assessed by WC, and risk of total prostate cancer (26). However, several studies which examined the association between visceral obesity and risk of aggressive prostate cancer reported positive findings (21, 27, 28). Two studies conducted exclusively among black men found a 2-fold increased risk of aggressive prostate cancer with elevated WC (10, 29). Our current study is the first, to our knowledge, to suggest that visceral obesity may be more strongly associated with aggressive prostate cancer in black men, relative to nonblack men. Our finding that subcutaneous adiposity, directly measured by SFA, is more strongly associated with aggressive prostate cancer among nonblack men requires validation in other studies. If future studies replicate this finding, it may provide further evidence that visceral obesity is more strongly associated with aggressive prostate cancer in black men, whereas subcutaneous adiposity is more strongly associated in nonblack men.

### Table 4. ORs for high-grade prostate cancer risk as a function of BMI, WC, SFA, VFA, and PPAT area

<table>
<thead>
<tr>
<th></th>
<th>All (n = 308)</th>
<th>Nonblack (n = 115)</th>
<th>Black (n = 193)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n OR (95% CI)</td>
<td>n OR (95% CI)</td>
<td>n OR (95% CI)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>64 1.00 (Ref.)</td>
<td>24 1.00 (Ref.)</td>
<td>40 1.00 (Ref.)</td>
</tr>
<tr>
<td>Overweight</td>
<td>110 0.90 (0.43–1.89)</td>
<td>44 1.08 (0.32–3.62)</td>
<td>66 0.84 (0.32–2.21)</td>
</tr>
<tr>
<td>Obese</td>
<td>73 1.03 (0.45–2.34)</td>
<td>23 1.43 (0.34–6.06)</td>
<td>50 0.96 (0.34–2.68)</td>
</tr>
<tr>
<td>Severely obese</td>
<td>61 2.97 (1.21–7.26)</td>
<td>24 2.54 (0.59–10.91)</td>
<td>37 3.71 (1.14–12.1)</td>
</tr>
<tr>
<td><strong>WC (cm)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (&lt;100)</td>
<td>102 1.00 (Ref.)</td>
<td>33 1.00 (Ref.)</td>
<td>69 1.00 (Ref.)</td>
</tr>
<tr>
<td>T2 (101–111)</td>
<td>103 1.27 (0.66–2.46)</td>
<td>42 1.12 (0.36–3.48)</td>
<td>61 1.29 (0.55–2.95)</td>
</tr>
<tr>
<td>T3 (≥112)</td>
<td>103 2.00 (1.02–3.92)</td>
<td>40 1.54 (0.48–4.92)</td>
<td>63 2.45 (1.04–5.77)</td>
</tr>
<tr>
<td><strong>SFA (cm²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (&lt;236)</td>
<td>102 1.00 (Ref.)</td>
<td>39 1.00 (Ref.)</td>
<td>63 1.00 (Ref.)</td>
</tr>
<tr>
<td>T2 (237–353)</td>
<td>103 1.35 (0.70–2.60)</td>
<td>47 1.12 (0.39–3.24)</td>
<td>56 1.52 (0.64–3.62)</td>
</tr>
<tr>
<td>T3 (≥354)</td>
<td>103 2.35 (1.19–4.65)</td>
<td>29 4.08 (1.05–15.91)</td>
<td>74 2.07 (0.91–4.71)</td>
</tr>
<tr>
<td><strong>VFA (cm²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (&lt;168)</td>
<td>102 1.00 (Ref.)</td>
<td>23 1.00 (Ref.)</td>
<td>79 1.00 (Ref.)</td>
</tr>
<tr>
<td>T2 (169–263)</td>
<td>103 1.16 (0.59–2.24)</td>
<td>41 0.46 (0.12–1.78)</td>
<td>62 1.30 (0.57–2.94)</td>
</tr>
<tr>
<td>T3 (≥264)</td>
<td>103 2.12 (1.07–4.22)</td>
<td>51 0.64 (0.18–2.24)</td>
<td>52 4.23 (1.67–10.69)</td>
</tr>
<tr>
<td><strong>PPAT area (cm²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1 (&lt;32)</td>
<td>102 1.00 (Ref.)</td>
<td>23 1.00 (Ref.)</td>
<td>79 1.00 (Ref.)</td>
</tr>
<tr>
<td>T2 (33–43)</td>
<td>103 1.05 (0.55–2.00)</td>
<td>42 0.24 (0.06–0.98)</td>
<td>62 1.61 (0.72–3.59)</td>
</tr>
<tr>
<td>T3 (≥44)</td>
<td>103 1.39 (0.70–2.76)</td>
<td>50 0.37 (0.08–1.60)</td>
<td>52 1.88 (0.80–4.44)</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ref, reference group; T, tertile. 
*Biopsy Gleason ≥7 versus <7.
Adjusted for age, race, PSA, clinical stage, duration of ADT, year of radiotherapy.
Consistent with other studies, we found that black men had reduced visceral adipose tissue compared with nonblack men, despite similar BMI and WC (6, 30). However, despite this reduced visceral adiposity, we found that visceral adipose tissue mass was more strongly associated with increased risk of aggressive prostate cancer in black men. Although this finding may appear counterintuitive, it is noteworthy that despite lower prevalence of visceral obesity on a population level, black men actually have increased risk of visceral obesity-associated comorbidities, including coronary heart disease, hypertension, stroke, and diabetes, relative to their white counterparts (12, 13). As such, the relationship between lower prevalence of visceral obesity but yet higher rates of visceral obesity-related comorbidities in black men mirrors the relationship between lower levels of visceral obesity but yet higher rates of aggressive prostate cancer in black men. To what degree racial differences in amount or function of visceral adipose tissue contribute to racial disparity in prostate cancer is not understood and requires further study. However, it has been shown that, despite reduced visceral adipose tissue, circulating levels of obesity-associated growth factors and proinflammatory adipokines are elevated in black men, whereas adiponectin levels are reduced (31–33). Given that these factors may contribute to the association between obesity and prostate cancer (4), future studies are warranted to explore the potential impact of race-specific differences in levels of obesity-associated growth factors and adipokines on the prostate cancer racial disparity.

Despite several in vitro studies which have reported that conditioned media from PPAT may promote an aggressive phenotype in prostate cancer cell lines (34–36); we found no association between elevated PPAT and increased risk of aggressive prostate cancer in our cohort of black and nonblack men. A previous study of 932 radiotherapy-treated patients with prostate cancer reported a significant association between high PPAT area and high-grade prostate cancer (OR 1.04; 95% CI, 1.03–1.06; ref. 11). However, a similar analysis conducted by the same group among lower risk, brachytherapy patients found no significant association between PPAT area and risk of aggressive prostate cancer (14). Thus, although larger epidemiologic studies are needed to examine the association between PPAT and risk of aggressive prostate cancer, these mixed results may suggest that PPAT is not the most important mediator of the link between obesity and risk of aggressive prostate cancer. In addition, as ours is the first study to report that black men have significantly less PPAT, relative to nonblack men, future studies should examine whether the PPAT inflammatory profile differs by race.

This study has several limitations that should be considered. All measures of obesity were obtained at the time of radiotherapy and thus, for men who received ADT, these measures were obtained post-ADT. Although ADT has been associated with significant weight gain in the first year of treatment (23, 37), the amount of weight gain after only 3 months of ADT has not been found to be significant (38). In our cohort, median duration of ADT use before radiotherapy was 2.48 months (IQR: 2.04–3.19) and, indeed, we did not find any association between duration of ADT and any measure of obesity, suggesting that any impact of ADT on our obesity measures was negligible. We lacked sufficient events for long-term outcomes such as prostate cancer-specific mortality; however, we examined Gleason score as an intermediate endpoint for aggressive disease given that Gleason score is the strongest predictor of prostate cancer-specific mortality in men newly diagnosed with localized prostate cancer (39). Future studies should explore alternative definitions of aggressive prostate cancer. Although central pathology review of biopsies was not available for this study, variations in Gleason grading between pathologists would likely be unrelated to obesity measures. Thus, this potential source of outcome misclassification would bias our results toward the null. Given that our cohort was limited to this convenience sample of radiotherapy-treated patients due to the availability of CT scans for adipose tissue quantification, it is important to consider that our results may not be representative of all patients with prostate cancer. To what degree our results apply to all men with prostate cancer remains to be determined by future studies. Finally, an important limitation of all cross-sectional studies is that causality cannot be inferred from these associations. Despite these limitations, our study exhibited a number of important strengths. Misclassification of adipose tissue distribution is a risk for studies relying on surrogate measures of obesity and may contribute to some of the variability in epidemiologic studies exploring the association between obesity and prostate cancer (28). Thus, an important strength of our study was accurate quantification of adipose tissue depots, enabling us to estimate more precisely the association between adipose tissue distribution and risk of aggressive prostate cancer. Finally, 63% of our cohort was black, enabling us to assess the impact of race on the association between obesity and risk of aggressive prostate cancer. In conclusion, in this cross-sectional study of radiotherapy-treated patients with prostate cancer, although elevated BMI and WC were associated with increased risk of aggressive prostate cancer in both races, we found that the association between visceral obesity, as measured by VFA, and increased risk of aggressive prostate cancer was restricted to black men. These hypothesis-generating data suggest that racial differences in adipose tissue distribution may contribute to the prostate cancer racial disparity and that visceral obesity may be particularly strongly associated with aggressive prostate cancer among black men. In addition, these findings may point to a potential mechanism that may be targeted to disrupt the obesity-aggressive prostate cancer link in black men. Together, these findings highlight the importance of considering racial differences in adipose tissue distribution when...
exploring the association between obesity and risk of aggressive prostate cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors’ Contributions

Conception and design: E.H. Allott, B.F. Koontz, J.K. Salama, S.J. Freedland


Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E.H. Allott, H.-J. Song, K.N. Sourbeer, J.K. Salama, S.J. Freedland

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E.H. Allott, L.E. Howard, S.J. Freedland

Writing, review, and/or revision of the manuscript: E.H. Allott, L.E. Howard, K.N. Sourbeer, B.F. Koontz, J.K. Salama, S.J. Freedland

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.N. Sourbeer

Study supervision: S.J. Freedland

Grant Support

This work was supported by NCI grant 5R25-CA126938-03 (to E.H. Allott) and NIH grants 1R01-CA131255-01A1 and 1K24CA160653 (to S.J. Freedland).

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Received March 4, 2014; revised July 18, 2014; accepted August 12, 2014; published OnlineFirst August 21, 2014.

References

20. Caire AA, Sun L, Polasik TJ, Albala DM, Moul JW. Obese African-Americans with prostate cancer (T1c and a prostate-specific antigen, PSA, level of <10 ng/mL) have higher-risk pathological features and a greater risk of PSA recurrence than non-African-Americans. BJU Int 2010;106:1157–60.
Racial Differences in Adipose Tissue Distribution and Risk of Aggressive Prostate Cancer among Men Undergoing Radiotherapy


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-14-0236

Cited articles
This article cites 39 articles, 7 of which you can access for free at:
http://cebp.aacrjournals.org/content/23/11/2404.full#ref-list-1

Citing articles
This article has been cited by 4 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/23/11/2404.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link
http://cebp.aacrjournals.org/content/23/11/2404.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.