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Abdominal and pelvic adipose tissue distribution and risk of prostate cancer recurrence after radiation therapy

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Abstract

Background: Fat distribution varies between individuals of similar body mass index (BMI). We hypothesized that visceral obesity is more strongly associated with poor prostate cancer outcomes than overall obesity defined by BMI.

Materials and Methods: We quantified abdominal visceral and subcutaneous fat area (VFA and SFA), and pelvic periprostatic adipose tissue area (PPAT), using computed tomography scans from radiation-treated prostate cancer patients at the Durham North Carolina Veterans Administration Hospital. Multivariable-adjusted Cox regression examined associations between each adiposity measure and risk of recurrence, overall and stratified by race and receipt of androgen deprivation therapy (ADT).

Results: Of 401 patients (59% black) treated from 2005 to 2011, 84 (21%) experienced recurrence during 9.3 years median follow-up. Overall, obesity defined by BMI was not associated with recurrence risk overall or stratified by race or ADT, nor was any measure of fat distribution related to the risk of recurrence overall or by race. However, higher VFA was associated with increased risk of recurrence in men who received radiation only (hazard ratio [HR], 1.79; 95% confidence interval [CI], 0.87-3.66), but inversely associated with recurrence risk in men treated with radiation and ADT (HR, 0.49; 95% CI, 0.24-1.03; *P*-interaction = .002), though neither association reached statistical significance. Similar patterns of ADT-stratified associations were observed for PPAT and SFA.

Conclusions: Associations between abdominal and pelvic adiposity measures and recurrence risk differed significantly by ADT receipt, with positive directions of association observed only in men not receiving ADT. If confirmed, our findings suggest that obesity may have varying effects on prostate cancer progression risk dependent on the hormonal state of the individual.

KEYWORDS

adipose tissue distribution, hormonal therapy, obesity, outcomes, periprostatic adipose tissue, prostate cancer

1 | INTRODUCTION

Prostate cancer is the most frequently diagnosed non-skin cancer among men in the United States.[1] Obesity is a risk factor linked with increased prostate cancer aggressiveness and a poorer prognosis. Specifically, obesity has been associated with an increased risk of biochemical recurrence following radical prostatectomy and external beam radiotherapy, higher frequency of metabolic complications and treatment failure after androgen deprivation therapy (ADT), and increased likelihood of prostate cancer-specific mortality.[2] Though studies in radiation-treated patients are relatively few, a secondary analysis of data from a randomized trial testing adjuvant vs salvage ADT in men treated with external beam radiation therapy found that larger body mass index (BMI) was associated with higher prostate cancer-specific mortality.[3] Understanding the association between obesity and aggressive prostate cancer has important public health implications as lifestyle interventions can influence this potentially modifiable risk factor.

Most studies to date have focused on the relationship between BMI, a measure of overall adiposity, and prostate cancer outcomes. Few have considered adipose tissue distribution measures, including visceral adipose tissue, a fat depot known to be more metabolically active than subcutaneous areas.[4] Also, most studies have examined associations between obesity and prostate cancer outcomes in white men. Black men have a lower quantity of visceral adipose tissue compared with other races,[5] but a higher prevalence of obesity-related metabolic disease.[6-8] Therefore, it is important to have a diverse study cohort to understand and account for potential racial differences in associations with prostate cancer outcomes.

We previously examined the relationship between adipose tissue distribution and tumor aggressiveness at diagnosis in a retrospective, racially diverse cohort of prostate cancer patients treated with primary radiation at the Durham North Carolina Veterans Administration Hospital.[9] To extend our previous analysis, the objective of this current study was to examine the association between obesity, adipose tissue distribution, and risk of prostate cancer recurrence, overall and stratified by race and by receipt of ADT. We hypothesized that excess visceral adiposity would be more strongly associated with poor prostate cancer outcomes than overall obesity, as defined by high BMI. We also examined periprostatic adipose tissue (PPAT), a type of visceral fat enveloping the prostate.[10]

2 | MATERIALS AND METHODS

2.1 | Study design

We identified a cohort of 407 men as a consecutive series of patients with biopsy-confirmed prostate cancer that were treated with primary external beam radiotherapy (XRT) or brachytherapy from 2005 to 2011 at the Durham Veterans Affairs (VA) Medical Center. We excluded 1 patient missing BMI data, 4 patients missing pre-biopsy prostate-specific antigen (PSA), and 1 patient missing follow-up data, resulting in a study cohort of 401 men.

2.2 | Adipose tissue measurement

Visceral fat area (VFA), subcutaneous fat area (SFA), and PPAT area were measured using radiotherapy planning computed tomography (CT) scans, as previously described.[9] Briefly, VFA and SFA were calculated using a single CT slice at the level of the L4/L5 vertebrae, a validated method used by other groups.[11-13] PPAT area was calculated using a single CT slice at the first anterior point of the pubic symphysis, as we and others have done previously.[9,14,15] To define PPAT area, the Eclipse drawing tool (Eclipse software, Varian Medical Systems) was used to contour a region ranging from the posterior pubic bone, along the lateral border of obturatorius internus muscle and anterior gluteus maximus muscle to the anterior coccyx bone. Pelvis size was defined as the total area of this contoured region, while PPAT was the total area of adipose tissue in this region. For all abdominal and pelvic fat measures, adipose tissue was differentiated from other tissues by thresholding on Hounsfield units (HU) −190 to −30 using Eclipse software (Varian Medical Systems). PPAT density ratio was calculated as PPAT area divided by pelvis size. Since waist circumference (WC) was not measured in clinic visits, it was determined retrospectively from the same CT slices used to calculate VFA and SFA. Given that the purpose of the CT scans was for radiotherapy planning, all 401 patients had CTs at the level of the prostate from which to obtain PPAT measures, but fewer had CTs available at L4/L5 from which to obtain abdominal adipose tissue measures (n = 321). As such, the analysis cohort for abdominal adipose tissue measures consisted of these 321 men only.

2.3 | Obesity definitions

Height and weight were measured at the closest medical visit before radiation therapy and were abstracted from patient medical records. These values were used to calculate BMI, which was categorized as greater than or equal to 30 vs less than 30 kg/m^2. According to the World Health Organization definitions, a BMI ≥ 30 is considered obese.[16] There are no clearly defined categories for VFA, SFA, WC, or PPAT. Therefore, adipose tissue measures were categorized as greater than or equal to median vs less than median for this cohort. We also considered continuous measures of each fat type, measured per unit standard deviation.

2.4 | Prostate cancer treatment and outcome definitions

According to the Phoenix definition,[17] PSA recurrence was defined as at least 2 ng/mL above the post-radiation PSA nadir. Recurrence was recorded on the date of the first PSA > 2 ng/mL above the nadir. Recurrence due to radiographic progression was defined as evidence of prostate cancer metastases on a scan in

TABLE 1 Demographic and clinical characteristics overall and by ADT use

	Overall (N = 401)	No ADT (N = 211)	ADT (N = 190)
Age, mean ± SD	63.9 (6.7)	63.1 (6.4)	64.9 (6.9)
Race			
Non-black	163 (41%)	81 (38%)	82 (43%)
Black	238 (59%)	130 (62%)	108 (57%)
BMI, kg/m^2, median (Q1-Q3)	29.0 (25.7-33.4)	30.0 (26.4, 34.5)	27.7 (25.1, 31.9)
Year of radiation, median (Q1-Q3)	2008 (2007-2009)	2008 (2007, 2009)	2008 (2007, 2009)
Follow-up, y, median (Q1-Q3)	9.3 (7.3-10.6)	9.5 (7.0-10.9)	9.1 (7.4-10.3)
Brachytherapy, n (%)	96 (24%)	69 (33%)	27 (14%)
ADT, n (%)			
None	211 (53%)	211 (100%)	0
Short-duration	118 (29%)	0	118 (62%)
Long-duration	72 (18%)	0	72 (38%)
Prostate TRUS volume, cm^3, median (Q1-Q3)	32 (24-45)	30.0 (24.0, 38.0)	35.0 (25.0, 49.0)
Positive biopsy cores, %, median (Q1-Q3)	33.3 (16.7-51.9)	25.0 (16.7, 44.4)	41.7 (18.2, 66.7)
PSA, ng/mL, median (Q1-Q3)	6.5 (4.9-11.0)	5.9 (4.7, 8.3)	8.8 (5.4, 16.5)
Biopsy grade group, n (%)			
1	169 (42%)	120 (57%)	49 (26%)
2-3	171 (43%)	86 (41%)	85 (45%)
4-5	61 (15%)	5 (2%)	56 (29%)
Clinical stage, n (%)			
T1	280 (70%)	168 (80%)	112 (59%)
T2/T3	121 (30%)	43 (20%)	78 (41%)

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; PSA, prostate-specific antigen; TRUS, transrectal ultrasonography.

the absence of PSA recurrence. Recurrence was recorded on the date of the scan. Recurrence due to treatment was defined as receiving either a radical prostatectomy after initial radiation, additional radiation more than 16 weeks after the start of initial radiation, or chemotherapy more than 6 months after the start of initial radiation. Recurrence was recorded on the date of initiation of salvage therapy. When determining the date of recurrence, definitions based on PSA recurrence or recurrence due to radiographic progression were prioritized over definitions based on recurrence due to treatment.

Among patients who received ADT as part of their initial radiation treatment, we categorized ADT use as either short-duration or long-duration. ADT was generally initiated 6 to 8 weeks before the start of radiation in both short-duration and long-duration users. ADT use was considered short-duration if it lasted less than or equal to 6 months. Long-duration ADT consisted of ADT use that was longer than 6 months (commonly 18-36 months total). We did not collect information regarding the type of ADT.

All-cause mortality was abstracted from the electronic health records. Prostate cancer-specific mortality was defined as dying with progressive, metastatic castration-resistant prostate cancer and no other obvious cause of death.

2.5 | Statistical analysis

Patient demographic and clinical characteristics were summarized among patients overall and stratified by ADT use. Cox proportional hazards models were used to test the association between each measure of adiposity (overall: BMI; visceral: WC and VFA; subcutaneous: SFA; and pelvic: PPAT area and PPAT density) and risk of recurrence, prostate cancer-specific mortality, and all-cause mortality. We treated recurrence as our primary outcome, with prostate cancer-specific mortality and all-cause mortality treated as secondary outcomes. Each adiposity measure was examined in separate models due to collinearity and was categorized as described above. Age-adjusted models were run as well as models adjusted for age (continuous), race (black and non-black), year of radiation (continuous), biopsy grade group (1, 2-3, 4-5), PSA (continuous, log-transformed), clinical stage (T1, T2/T3), and ADT (none, short-duration, and long-duration). Due to a low number of events, only an age-adjusted analysis was run for the prostate cancer-specific mortality outcome.

In a secondary analysis, models for recurrence were re-run stratified by race and the interaction between race and each adiposity measure was tested using a Wald test. Similarly, we stratified

analyses for the recurrence outcome by receipt of ADT and the interactions between ADT use and each adiposity measure were tested.

SAS 9.4 (SAS Institute Inc., Cary, NC) was used for statistical analyses. $P < .05$ was considered statistically significant.

3 | RESULTS

The mean (SD) age of our study cohort at diagnosis was 63.9 (6.7) years and 238 (59%) men were black (Table 1). Median BMI was 29.0 kg/m^2 (interquartile range; IQR 25.7-33.4) and median follow-up was 9.3 years (IQR 7.3-10.6). Roughly half of the cohort (n = 190; 47%) received ADT in addition to radiation, the majority of whom received short-duration ADT (ie, less than 6 months duration; n = 118; 62%). The distribution of grade groups 1, 2 to 3, and 4 to 5 were 169 (42%), 171 (43%), and 61 (15%), respectively. There were 280 (70%) patients with clinical stage T1 and 121 (30%) with stage T2 or T3 prostate cancer. Table 1 also shows patient characteristics stratified by ADT use. Men who received ADT alongside radiation were slightly older at diagnosis (64.9 vs 63.1 years) but had similar follow-up time. They were less likely to have brachytherapy than men who did not receive ADT (14% vs 33%). Men who received ADT tended to have more aggressive tumors than men who did not, as evidenced by a higher percentage of positive biopsy cores, higher PSA, and higher tumor grade and stage.

During follow-up, 84 patients experienced a recurrence and 138 died, of whom 21 died from prostate cancer. There was no relationship between any adiposity measure and risk of recurrence, prostate cancer-specific mortality, or all-cause mortality, on either age-adjusted analysis or after adjusting for demographic and clinical characteristics (Table 2). When stratified by race, similar, non-significant results for the association between adiposity measures and risk of recurrence were seen in black men compared with non-black men (Table 3). When adiposity measures were modeled as continuous variables per standard deviation unit, again we found no associations between adiposity measures and any outcomes (data not shown).

Despite these null findings overall, we found statistically significant interactions between ADT use and WC ($P = .025$), VFA ($P = .002$), SFA ($P = .010$), PPAT area ($P = .002$), PPAT density ($P = .002$), but not BMI ($P = .12$), in predicting risk of recurrence. Thus, given this evidence for ADT acting as an effect modifier of the association between adiposity measures and recurrence risk, models were stratified by ADT use. Among men who did not receive ADT, multivariable-adjusted hazard ratios (HRs) for the association between WC, VFA, SFA, PPAT area, and PPAT density and recurrence ranged from 1.17 to 1.79, indicating a positive association between higher adiposity measures and increased risk of recurrence, although none reached statistical significance (Table 4). In contrast, among men who did receive ADT, the multivariable-adjusted HRs for associations between WC, VFA, SFA, PPAT area, and PPAT density and recurrence ranged from 0.46 to 0.83, indicating an inverse association between higher adiposity and risk of recurrence, although again these did not reach statistical significance, with the exception of PPAT area (Table 4). There was no association between BMI and risk of recurrence in men who did (HR, 0.97; 95% CI, 0.48-1.94) or did not receive ADT (HR, 0.90; 95% CI, 0.50-1.62).

4 | DISCUSSION

Visceral obesity may be a better measure of a metabolically unhealthy obesity phenotype than BMI,[18] but relatively few prostate cancer studies to date have incorporated measures of visceral obesity. Leveraging planning CT scans to accurately quantify adipose tissue distribution in this study of radiotherapy-treated prostate cancer patients, we found no significant associations between any measure of overall, visceral or subcutaneous, or pelvic adiposity, and risk of recurrence. However, in an a priori stratified analysis, though not statistically significant, we found positive associations between higher adiposity measures and risk of recurrence in men not using ADT. Conversely, though again not statistically significant, directions of association between higher adiposity measures and recurrence risk were inverse in men treated with radiation and ADT. If confirmed, these findings suggest that ADT may play a role in modifying the effects of obesity on prostate cancer outcomes.

Obesity, as measured by BMI, has been associated with increased prostate cancer mortality.[2,3] However, the role of adipose tissue distribution in prostate cancer outcomes is less clear. One study of 112 eligible men treated with radiotherapy found that there was no association between obesity measures (visceral and subcutaneous adipose tissues, WC, or BMI) and biochemical failure.[19] Consistent with this study, we found no significant association between overall, visceral, subcutaneous or pelvic adiposity measures and risk of recurrence, prostate cancer-specific mortality, or all-cause mortality. However, other studies did find associations between adiposity measures and prostate cancer outcomes. One retrospective study used CT imaging to assess adipose tissue characteristics and predict biochemical recurrence in 171 men treated with radiotherapy. This study concluded that higher subcutaneous adipose tissue density, measured in Hounsfield units, was associated with a higher rate of biochemical failure for men with high-risk prostate cancer.[20] In addition, the only prospective study to date that directly measured fat distribution and examined its relationship with risk of advanced and fatal prostate cancer was a longitudinal study among Icelandic men. This study prospectively evaluated adipose tissue distribution using CT scans and found that BMI and WC were associated with increased risk of both advanced and fatal disease. Visceral adiposity was associated with a higher risk of advanced prostate cancer, while higher amounts of thigh subcutaneous fat was associated with increased risk of fatal prostate cancer.[11] Our results, along with these mixed findings from other studies, suggest that more research incorporating accurate measures of adipose tissue distribution is needed to better understand the link between obesity and prostate cancer outcomes.

TABLE 2 Hazard ratios and 95% confidence intervals for associations between measures of adiposity and risk of recurrence, prostate cancer-specific mortality, and all-cause mortality

	Recurrence			Prostate cancer-specific mortality			All-cause mortality		
	N_e (N)	HR[a] (95% CI)	HR[b] (95% CI)	N_e (N)	HR[a] (95% CI)	HR[b] (95% CI)	N_e (N)	HR[a] (95% CI)	HR[b] (95% CI)
BMI, kg/m^2									
<30	47/229	Ref	Ref	12/229	Ref	Ref	87/229	Ref	Ref
≥30	37/172	1.05 (0.68-1.62)	0.99 (0.64-1.55)	9/172	1.07 (0.45-2.57)	⋯	51/172	0.83 (0.59-1.18)	0.80 (0.56-1.15)
WC, cm									
<Median[c]	36/160	Ref	Ref	12/160	Ref	Ref	64/160	Ref	Ref
≥Median[c]	37/161	1.06 (0.67-1.67)	1.01 (0.63-1.61)	8/161	0.66 (0.27-1.62)	⋯	52/161	0.81 (0.56-1.16)	0.78 (0.54-1.14)
VFA, cm^2									
<Median[c]	36/160	Ref	Ref	9/160	Ref	Ref	60/160	Ref	Ref
≥Median[c]	37/161	1.09 (0.69-1.72)	1.00 (0.62-1.61)	11/161	1.26 (0.52-3.04)	⋯	56/161	0.95 (0.66-1.37)	0.94 (0.64-1.37)
SFA, cm^2									
<Median[c]	33/160	Ref	Ref	10/160	Ref	Ref	66/160	Ref	Ref
≥Median[c]	40/161	1.14 (0.72-1.80)	1.12 (0.70-1.79)	10/160	0.95 (0.40-2.30)	⋯	50/151	0.73 (0.51-1.06)	0.71 (0.49-1.04)
PPAT area, cm^2									
<Median[c]	45/200	Ref	Ref	13/200	Ref	Ref	69/200	Ref	Ref
≥Median[c]	39/201	0.96 (0.63-1.48)	0.91 (0.58-1.45)	8/201	0.67 (0.28-1.62)	⋯	69/201	1.11 (0.80-1.56)	1.09 (0.76-1.57)
PPAT density									
<Median[c]	44/200	Ref	Ref	14/200	Ref	Ref	71/200	Ref	Ref
≥Median[c]	40/201	1.00 (0.65-1.54)	0.97 (0.62-1.52)	7/201	0.53 (0.21-1.30)	⋯	67/201	1.01 (0.72-1.41)	1.00 (0.71-1.43)

Note: N_e, number of events; N, total number of cases.

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; PPAT, periprostatic adipose tissue; PSA, prostate-specific antigen; SFA, subcutaneous fat area; VFA, visceral fat area; WC, waist circumference.

[a]Age-adjusted models adjusted for age only.

[b]Multivariable models adjusted for age, race, year, biopsy grade group, PSA, clinical stage, and ADT (none, short-duration, long-duration).

[c]The median value is 104.56 cm for WC, 217.64 cm^2 for VFA, 287.32 cm^2 for SFA, 36.44 cm^2 for PPAT area, and 0.36 for PPAT density.

TABLE 3 Hazard ratios and 95% confidence intervals for associations between measures of adiposity and risk of recurrence, stratified by race

	Black men			Non-black men			
	N_e (N)	HR[a] (95% CI)	HR[b] (95% CI)	N_e (N)	HR[a] (95% CI)	HR[b] (95% CI)	*P*-interaction[c]
BMI, kg/m^2							
<30	25/132	Ref	Ref	22/97	Ref	Ref	
≥30	24/106	1.20 (0.68-2.11)	0.98 (0.55-1.77)	13/66	0.86 (0.43-1.72)	0.74 (0.36-1.49)	.42
WC, cm							
<Median[d]	20/102	Ref	Ref	16/58	Ref	Ref	
≥Median[d]	24/98	1.35 (0.74-2.44)	1.14 (0.62-2.11)	13/63	0.71 (0.34-1.47)	0.57 (0.27-1.22)	.15
VFA, cm^2							
<Median[d]	25/116	Ref	Ref	11/44	Ref	Ref	
≥Median[d]	19/84	1.15 (0.63-2.10)	1.02 (0.55-1.89)	18/77	0.92 (0.43-1.95)	0.87 (0.39-1.93)	.83
SFA, cm^2							
<Median[d]	19/99	Ref	Ref	14/61	Ref	Ref	
≥Median[d]	25/101	1.26 (0.69-2.29)	1.15 (0.62-2.13)	15/60	0.96 (0.46-2.00)	0.77 (0.36-1.64)	.36
PPAT area, cm^2							
<Median[d]	29/136	Ref	Ref	16/64	Ref	Ref	
≥Median[d]	20/102	0.99 (0.56-1.75)	0.91 (0.50-1.66)	19/99	0.92 (0.47-1.79)	0.86 (0.42-1.79)	.93
PPAT density							
<Median[d]	27/137	Ref	Ref	17/63	Ref	Ref	
≥Median[d]	22/101	1.18 (0.67-2.08)	1.14 (0.64-2.05)	18/100	0.77 (0.40-1.51)	0.74 (0.35-1.55)	.52

Note: N_e, number of events; N, total number of cases.

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; PPAT, periprostatic adipose tissue; PSA, prostate-specific antigen; SFA, subcutaneous fat area; VFA, visceral fat area; WC, waist circumference.

[a]Age-adjusted models adjusted for age only.

[b]Multivariable models adjusted for age, year, biopsy grade group, PSA, clinical stage, and ADT (none, short-duration, long-duration).

[c]*P* value for the interaction between race and each adiposity measure in predicting risk of recurrence.

[d]The median value is 104.56 cm for WC, 217.64 cm^2 for VFA, 287.32 cm^2 for SFA, 36.44 cm^2 for PPAT area, and 0.36 for PPAT density.

The mechanisms contributing to the association between obesity and prostate cancer aggressiveness and progression are not completely understood. Obesity is a heterogeneous phenotype and individuals with similar BMI can vary greatly in their metabolic profile, highlighting the importance of understanding adipose tissue distribution. For example, visceral adipose tissue has higher expression of glucocorticoid and androgen receptors, is more metabolically active, and has higher levels of lipolysis than subcutaneous areas.[4] Inflammatory cells, producing chemokines such as monocyte chemoattractant protein-1 (MCP-1), are more prevalent in visceral fat compared with subcutaneous fat.[21] Furthermore, visceral adipose tissue is negatively correlated with bioavailable testosterone[22] which has been linked with prostate cancer risk in some[23-25] but not all[26,27] studies. As such, measuring adipose tissue distribution and, in particular, visceral adiposity may be key to improving our understanding of the relationship between obesity and prostate cancer outcomes.

One of our hypotheses focused on PPAT due to previous in vitro research that showed that coculture with PPAT produced an aggressive phenotype in prostate cancer cells.[28,29] One study used magnetic resonance spectroscopy and found that the fatty acid composition was altered in PPAT of patients with aggressive prostate cancer.[30] When observing secretions from PPAT explants, PPAT-conditioned media from more obese patients caused significantly more proliferation of prostate cancer and endothelial cells in vitro than PPAT-conditioned media obtained from leaner men.[31] Other research using gene expression of PPAT found that PPAT of obese men had higher metalloproteinase activity, which contributes to immunoinflammatory responses and ultimately promotes oncogenesis.[32] Although some epidemiological data support a relationship between PPAT and prostate cancer aggressiveness,[14,33] only one study before the current study, to our knowledge, examined the association of PPAT with prostate cancer outcomes. This study, among men receiving primary ADT, found that PPAT volume was significantly higher in patients who developed castration-resistant prostate cancer.[34] In contrast, although we did not study castration-resistant prostate cancer, we found no association between PPAT and prostate cancer recurrence or mortality. Given the extremely few studies in this area, more are needed to determine if knowledge of PPAT area could inform prostate cancer prognosis.

Our findings from prespecified secondary analysis suggest that abdominal and pelvic obesity may have varying effects on prostate cancer progression depending on the receipt of ADT. Specifically,

TABLE 4 Hazard ratios and 95% confidence intervals for associations between measures of adiposity and risk of recurrence, stratified by ADT use

	No ADT use			ADT use			
	N_e (N)	HR[a] (95% CI)	HR[b] (95% CI)	N_e (N)	HR[a] (95% CI)	HR[b] (95% CI)	*P*-interaction[c]
BMI, kg/m^2							
<30	23/105	Ref	Ref	24/124	Ref	Ref	
≥30	24/106	1.07 (0.60-1.89)	0.90 (0.50-1.62)	13/66	0.98 (0.50-1.94)	0.97 (0.48-1.94)	.12
WC, cm							
<Median[d]	15/68	Ref	Ref	21/92	Ref	Ref	
≥Median[d]	23/85	1.23 (0.64-2.36)	1.17 (0.60-2.30)	14/76	0.91 (0.46-1.80)	0.83 (0.42-1.67)	.025
VFA, cm^2							
<Median[d]	14/70	Ref	Ref	22/90	Ref	Ref	
≥Median[d]	24/83	1.60 (0.83-3.10)	1.79 (0.87-3.66)	13/78	0.71 (0.36-1.42)	0.49 (0.24-1.03)	.002
SFA, cm^2							
<Median[d]	13/70	Ref	Ref	20/90	Ref	Ref	
≥Median[d]	25/83	1.59 (0.80-3.16)	1.47 (0.72-2.98)	15/78	0.88 (0.45-1.72)	0.85 (0.43-1.69)	.010
PPAT area, cm^2							
<Median[d]	23/113	Ref	Ref	22/87	Ref	Ref	
≥Median[d]	24/98	1.55 (0.87-2.76)	1.33 (0.71-2.48)	15/103	0.54 (0.28-1.03)	0.46 (0.23-0.93)	.002
PPAT density							
<Median[d]	22/110	Ref	Ref	22/90	Ref	Ref	
≥Median[d]	25/101	1.56 (0.87-2.80)	1.31 (0.71-2.43)	15/100	0.55 (0.29-1.07)	0.54 (0.27-1.06)	.002

Note: N_e, number of events; N, total number of cases.

Abbreviations: ADT, androgen deprivation therapy; BMI, body mass index; PPAT, periprostatic adipose tissue; PSA, prostate-specific antigen; SFA, subcutaneous fat area; VFA, visceral fat area; WC, waist circumference.

[a]Age-adjusted models adjusted for age only.

[b]Multivariable models adjusted for age, race, year, biopsy grade group, PSA, and clinical stage.

[c]*P* value for the interaction between race and each adiposity measure in predicting risk of recurrence.

[d]The median value is 104.56 cm for WC, 217.64 cm^2 for VFA, 287.32 cm^2 for SFA, 36.44 cm^2 for PPAT area, and 0.36 for PPAT density.

though not statistically significant, positive associations between measures of adiposity and prostate cancer outcomes were observed in men who did not receive ADT, while inverse associations were seen in men who received ADT. Whether these opposite directions of association are the result of ADT acting as a true modifier of the obesity-prostate cancer link, or a result of potential exposure misclassification due to ADT-related changes to adipose tissue distribution, remains to be determined. Considering the latter, it is possible that our measures of obesity, which were taken 6 to 8 weeks after the initiation of ADT in men who received this treatment, were affected by ADT-related changes to the individual's hormonal state resulting in altered adipose tissue quantity and distribution. ADT is known to cause body composition changes,[35] so our measures of obesity might not accurately reflect pretreatment obesity levels in men on ADT and instead reflect obesity as a consequence of ADT. Declining testosterone levels, achieved with ADT, correlate with increasing body fat accumulation and decreasing lean body mass.[36] ADT is also related to metabolic changes such as decreasing insulin sensitivity and increasing low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides.[37] Another factor that may have contributed to significant differences in associations between obesity and outcomes by ADT is that tumor characteristics varied by ADT. Men receiving ADT had more aggressive tumors than those who received radiation alone and the effect of obesity on outcomes in these men may be masked by the more aggressive clinical course of their disease.

Our observation that associations between obesity and prostate cancer outcomes varied significantly by ADT use could have a biological explanation. To our knowledge, no studies have investigated associations between obesity and prostate cancer outcomes and how they may vary by receipt of hormone therapy. However, in a meta-analysis that looked at obesity and breast cancer by hormone therapy, there was a stronger association between obesity and postmenopausal breast cancer risk in women not using estrogen-progestin therapy.[38] It has been proposed that exogenous hormones provided by estrogen-progestin therapy may mask the effect of altered levels of endogenous hormones in obesity, thereby blocking the effect of obesity on breast cancer risk. Among women using estrogen-progestin therapy, estrogen levels are elevated. Therefore, the relative impact of adipose tissue estrogen production on the tumor is expected to be reduced.[38] Similarly, in prostate cancer, ADT could offset the effect of obesity-related disrupted endogenous hormone levels on tumor cells, thereby masking the association between obesity and prostate cancer outcomes in men receiving ADT. This hypothesis supports our findings of positive associations between obesity and recurrence only in men not using

ADT. However, given that this is the first study to test this hypothesis in prostate cancer, more research is necessary to determine if hormone therapy could modify associations between obesity and outcomes in prostate cancer patients.

This study has several limitations and strengths that should be considered. For example, despite the relatively long follow-up (median of 9.3 years) there was a relatively low number of events, specifically for outcomes such as prostate cancer-specific mortality, which led us to use recurrence as the primary outcome. Also, the cohort was composed of patients treated with radiation due to the availability of planning CT scans for determining adipose tissue measurements. Therefore, this may limit generalizability of our results when looking at all patients with prostate cancer undergoing various treatment regimens. Future studies are necessary to determine how outcomes in different treatment groups are affected by adipose tissue distribution. One major strength of this study is the racially diverse population. The cohort was 59% black, which allowed for more generalizability and unique contrasts to previous studies with cohorts that were predominantly made up of white men.

In conclusion, most findings in this study of radiotherapy-treated patients were null, such as associations between adiposity measures and risk of recurrence. However, in secondary analyses, we found that abdominal and pelvic obesity may have varying effects on prostate cancer outcomes depending on the hormonal state of the individual. These results merit exploration in future studies and if confirmed may have important clinical implications as well as provide further biological insights. Studying adipose tissue distribution and interaction with prostate cancer treatments will improve our understanding of the mechanisms associated with obesity and prostate cancer outcomes, which in turn will be important for developing future interventions to break the obesity-prostate cancer link.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin*. 2019;69:7-34.
2. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. *Eur Urol*. 2013;63:800-809.
3. Efstathiou JA, Bae K, Shipley WU, et al. Obesity and mortality in men with locally advanced prostate cancer: analysis of RTOG 85-31. *Cancer*. 2007;110:2691-2699.
4. Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. *Obes Rev*. 2010;11:11-18.
5. Neeland IJ, Ayers CR, Rohatgi AK, et al. Associations of visceral and abdominal subcutaneous adipose tissue with markers of cardiac and metabolic risk in obese adults. *Obesity (Silver Spring)*. 2013;21:E439-E447.
6. Chang SH, Pollack LM, Colditz GA. Life years lost associated with obesity-related diseases for U.S. non-smoking adults. *PLOS One*. 2013;8:e66550.
7. Cowie CC, Rust KF, Ford ES, et al. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. *Diabetes Care*. 2009;32:287-294.
8. Cossrow N, Falkner B. Race/ethnic issues in obesity and obesity-related comorbidities. *J Clin Endocrinol Metab*. 2004;89:2590-2594.
9. Allott EH, Howard LE, Song HJ, et al. Racial differences in adipose tissue distribution and risk of aggressive prostate cancer among men undergoing radiotherapy. *Cancer Epidemiol Biomarkers Prev*. 2014;23:2404-2412.
10. Toren P, Venkateswaran V. Periprostatic adipose tissue and prostate cancer progression: new insights into the tumor microenvironment. *Clin Genitourin Cancer*. 2014;12:21-26.
11. Dickerman BA, Torfadottir JE, Valdimarsdottir UA, et al. Body fat distribution on computed tomography imaging and prostate cancer risk and mortality in the AGES-Reykjavik study. *Cancer*. 2019;125:2877-2885.
12. Kvist H, Chowdhury B, Grangard U, Tylen U, Sjostrom L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. *Am J Clin Nutr*. 1988;48:1351-1361.
13. Ross R, Leger L, Morris D, de Guise J, Guardo R. Quantification of adipose tissue by MRI: relationship with anthropometric variables. *J Appl Physiol*. 1985;1992(72):787-795.
14. van Roermund JG, Bol GH, Witjes JA, Ruud Bosch JL, Kiemeney LA, van Vulpen M. Periprostatic fat measured on computed tomography as a marker for prostate cancer aggressiveness. *World J Urol*. 2010;28:699-704.
15. Zhai TS, Jin L, Hu LT, et al. Impact of peri-prostatic fat measurements using MRI on the prediction of prostate cancer with transrectal ultrasound-guided biopsy. *Urol Oncol*. 2020;38(2):37e1-e37, e39.
16. World Health Organization. https://www.who.int/topics/obesity/en/. Accessed 10/6/2019.
17. Roach M 3rd, Hanks G, Thames H Jr., et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65:965-974.
18. Kang YM, Jung CH, Cho YK, et al. Visceral adiposity index predicts the conversion of metabolically healthy obesity to an unhealthy phenotype. *PLOS One*. 2017;12:e0179635.
19. Zilli T, Nguyen TV, Bahary JP, Chagnon M, Dufresne A, Taussky D. Prognostic impact of abdominal adiposity, waist circumference and body mass index in patients with intermediate-risk prostate cancer treated with radiotherapy. *Int J Obes (Lond)*. 2011;35:1421-1426.
20. McDonald AM, Fiveash JB, Kirkland RS, et al. Subcutaneous adipose tissue characteristics and the risk of biochemical recurrence in men with high-risk prostate cancer. *Urol Oncol*. 2017;35(11):663e15-663, e21.
21. Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte chemoattractant protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophages resident in the AT. *J Clin Endocrinol Metab*. 2005;90:2282-2289.
22. Nielsen TL, Hagen C, Wraae K, et al. Visceral and subcutaneous adipose tissue assessed by magnetic resonance imaging in relation to circulating androgens, sex hormone-binding globulin, and luteinizing hormone in young men. *J Clin Endocrinol Metab*. 2007;92:2696-2705.

23. Park J, Cho SY, Jeong SH, Lee SB, Son H, Jeong H. Low testosterone level is an independent risk factor for high-grade prostate cancer detection at biopsy. *BJU Int*. 2016;118:230-235.
24. Shin BS, Hwang EC, Im CM, et al. Is a decreased serum testosterone level a risk factor for prostate cancer? A cohort study of Korean men. *Korean J Urol*. 2010;51:819-823.
25. Schatzl G, Madersbacher S, Thurridl T, et al. High-grade prostate cancer is associated with low serum testosterone levels. *Prostate*. 2001;47:52-58.
26. Morote J, Ramirez C, Gómez E, et al. The relationship between total and free serum testosterone and the risk of prostate cancer and tumour aggressiveness. *BJU Int*. 2009;104:486-489.
27. Muller RL, Gerber L, Moreira DM, Andriole G, Castro-Santamaria R, Freedland SJ. Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the Reduction by Dutasteride of Prostate Cancer Events trial. *Eur Urol*. 2012;62:757-764.
28. Laurent V, Guérard A, Mazerolles C, et al. Periprostatic adipocytes act as a driving force for prostate cancer progression in obesity. *Nat Commun*. 2016;7:10230.
29. Finley DS, Calvert VS, Inokuchi J, et al. Periprostatic adipose tissue as a modulator of prostate cancer aggressiveness. *J Urol*. 2009;182:1621-1627.
30. Iordanescu G, Brendler C, Crawford SE, Wyrwicz AM, Venkatasubramanian PN, Doll JA. MRS measured fatty acid composition of periprostatic adipose tissue correlates with pathological measures of prostate cancer aggressiveness. *J Magn Reson Imaging: JMRI*. 2015;42:651-657.
31. Venkatasubramanian PN, Brendler CB, Plunkett BA, et al. Periprostatic adipose tissue from obese prostate cancer patients promotes tumor and endothelial cell proliferation: a functional and MR imaging pilot study. *Prostate*. 2014;74:326-335.
32. Ribeiro R, Monteiro C, Cunha V, et al. Human periprostatic adipose tissue promotes prostate cancer aggressiveness in vitro. *J Exp Clin Cancer Res: CR*. 2012;31:32.
33. Dahran N, Szewczyk-Bieda M, Wei C, Vinnicombe S, Nabi G. Normalized periprostatic fat MRI measurements can predict prostate cancer aggressiveness in men undergoing radical prostatectomy for clinically localised disease. *Sci Rep*. 2017;7:4630.
34. Salji M, Hendry J, Patel A, Ahmad I, Nixon C, Leung HY. Periprostatic fat volume measurement as a predictive tool for castration resistance in advanced prostate cancer. *Eur Urol Focus*. 2018;4:858-866.
35. Haseen F, Murray LJ, Cardwell CR, O'Sullivan JM, Cantwell MM. The effect of androgen deprivation therapy on body composition in men with prostate cancer: systematic review and meta-analysis. *J Cancer Surviv*. 2010;4:128-139.
36. van Londen GJ, Levy ME, Perera S, Nelson JB, Greenspan SL. Body composition changes during androgen deprivation therapy for prostate cancer: a 2-year prospective study. *Crit Rev Oncol Hematol*. 2008;68:172-177.
37. Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. *J Urol*. 2013;189:S34-S42; discussion S43-4.
38. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev*. 2014;36:114-136.

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