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Overall and central obesity and prostate cancer risk in African men

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Abstract

Purpose African men are disproportionately affected by prostate cancer (PCa). Given the increasing prevalence of obesity in Africa, and its association with aggressive PCa in other populations, we examined the relationship of overall and central obesity with risks of total and aggressive PCa among African men.

Methods Between 2016 and 2020, we recruited 2,200 PCa cases and 1,985 age-matched controls into a multi-center, hospital-based case–control study in Senegal, Ghana, Nigeria, and South Africa. Participants completed an epidemiologic questionnaire, and anthropometric factors were measured at clinic visit. Multivariable logistic regression was used to examine associations of overall and central obesity with PCa risk, measured by body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR), respectively.

Results Among controls 16.4% were obese (BMI ≥ 30 kg/m^2), 26% and 90% had WC > 97 cm and WHR > 0.9, respectively. Cases with aggressive PCa had lower BMI/obesity in comparison to both controls and cases with less aggressive PCa, suggesting weight loss related to cancer. Overall obesity (odds ratio: OR = 1.38, 95% CI 0.99–1.93), and central obesity (WC > 97 cm: OR = 1.60, 95% CI 1.10–2.33; and WHtR > 0.59: OR = 1.68, 95% CI 1.24–2.29) were positively associated with D'Amico intermediate-risk PCa, but not with risks of total or high-risk PCa. Associations were more pronounced in West versus South Africa, but these differences were not statistically significant.

Discussion The high prevalence of overall and central obesity in African men and their association with intermediate-risk PCa represent an emerging public health concern in Africa. Large cohort studies are needed to better clarify the role of obesity and PCa in various African populations.

Keywords Prostate cancer · African men · Body mass index · Obesity · Central adiposity · Sub-Saharan Africa

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed solid tumor and the sixth leading cause of cancer deaths among men worldwide [1, 2]. In 2018, about 1.3 million men were diagnosed with PCa, and 360,000 men died from it [1]. Incidence and mortality rates of PCa vary significantly by race/ethnicity and by geographic region [1–3]. African American and Afro-Caribbean men have the highest PCa incidence and mortality rates in the world [2, 4]. Prostate cancer risk in African men is less clear. Despite potential underreporting of PCa in Africa

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[3, 5], the most recent estimates from the International Agency for Research on Cancer indicate an age-adjusted PCa incidence rate of 84.5 per 100,000 person-year for African men [2, 4, 6]. In comparison, current age-adjusted PCa incidence rates among US black men are 175.2 per 100,000 men [4]. Recent data suggest that PCa mortality rates among African men are among the highest in the world [1, 2, 4], suggesting that PCa in this population is either diagnosed at advanced stage due to limited access to health care and PCa screening, or has an unusually aggressive pattern. The World Health Organization (WHO) estimated that the annual number of deaths from PCa in Africa is expected to increase from 42,298 in 2018 to 94,909 in 2040, a 124.4% increase in the next two decades [7]. This increase is higher than those estimated for North America (+ 101.2%), Europe (+ 58.3%), and Asia (+ 105.6%) [7].

Despite the high incidence of PCa worldwide, other than age, family history of PCa, and race/ethnicity [8, 9], few etiological factors have been established. Obesity, usually defined as a body mass index (BMI) ≥ 30 kg/m^2, has been linked to PCa, but it is more consistently associated with PCa mortality and aggressiveness than with overall PCa incidence [10–12]. For example, in a large meta-analysis of 17 cohort studies including 76,978 cases, obesity was not associated with total PCa risk, but was associated with statistically significant 14% and 24% increased risks of aggressive cancer and PCa-specific mortality, respectively [10]. The Pooling Project of Prospective Studies of Diet and Cancer recently reported positive associations between baseline BMI and risks of advanced PCa [hazard ratio (HR) = 1.30, 95% CI 0.95–1.78] and PCa-specific mortality (HR = 1.52, 95% CI 1.12–2.07) when comparing BMI ≥ 35.0 versus 21–22.9 kg/m^2 [13]. In this study, waist circumference (WC) and waist-to-hip ratio (WHR), were also associated with 14% and 16% increased risks of high-grade PCa, respectively [13]. Unlike BMI, these measures reflect adipose tissue accumulation in the abdominal region [14]. Several studies, although not all, have suggested that central obesity, measured by WC, WHR, or waist–height ratio (WHtR), is more consistently associated with risks of overall PCa or more aggressive cancer compared to BMI [13, 15–22].

Noting the increasing prevalence of obesity in sub-Saharan Africa (SSA) [23, 24], as well as the rising incidence of PCa in this region [1, 2], we investigated the relationships of overall obesity/BMI and central obesity measurements (e.g., WC, WHR and WHtR) with risks of total PCa and more aggressive cancer in a large, multi-center, hospital-based case–control study of patients recruited in Senegal, Ghana, Nigeria, and South Africa through the Men of African Descent and Carcinoma of the Prostate (MADCaP) consortium.

Materials and methods

Study population and recruitment

The MADCaP is an international consortium established to investigate genetic and epidemiological risk factors of PCa among men of African ancestry [25]. For this study, the MADCaP team included researchers in seven tertiary-care hospitals and their affiliated universities in West and South Africa and four twinning centers at US universities.

Men aged 30 years or older, who resided in the catchment areas defined by the seven tertiary-care hospital centers between 2016 and 2020 and reported no European, Middle Eastern, or Asian grandparents or parents were eligible for recruitment. We excluded men who had any prior cancer diagnoses, except for non-melanoma skin cancer. All centers used common standardized protocols for subjects' recruitment, interviews, and data collection and processing [25, 26].

Prostate cancer cases

Men diagnosed with histologically confirmed PCa within the 6-month period prior to the date of study enrollment at each center, were eligible and recruited through Departments of Urology and Oncology at participating hospitals. In fact, this eligibility criterion applied mostly to PCa patients recruited during the first year (i.e., 2016) of the study period; all subsequently enrolled cases were newly diagnosed PCa patients. The median time between PCa diagnosis and recruitment into the study for all PCa cases was 29 days (0.98 months), and the interquartile range (IQR) was from 13 days (0.43 months) to 47 days (1.57 months). However, for cases enrolled in the first year of the study period, the median interval between PCa diagnosis and recruitment was 69 days (2.3 months) and the IQR was 34 days (1.13 months) to 144 days (4.8 months). Physicians in the participating departments reviewed medical charts to confirm PCa diagnoses and pathological tumor characteristics.

Controls

Men with no history of PCa or other cancers, who were seen for other conditions or diseases in the departments not affiliated with urology or oncology at participating tertiary-care hospitals, and who resided in the same catchment area as cases were recruited as controls [25]. The main hospital departments for recruitment of controls were Internal Medicine (including Cardiology), Family Medicine, General Surgery (not including Urology), Ophthalmology, and Orthopedics. Controls were frequency matched to PCa cases within each hospital by 5-year age group, and participating

center. The study protocol and procedures were approved by the Institutional Ethical Review Boards (IRBs) of all participating institutions. All cases and controls provided written informed consent to participate in the study. The participation rates/proportions ranged from 89% to 100% in PCa cases, and 85%–99% in controls across seven participating hospitals. However, overall, 95% of both eligible cases and controls agreed to participate and completed the study protocol and procedures.

Data collection

Interview

All study participants completed an epidemiological questionnaire through an in-person interview that collected detailed information on demographics (e.g., age, ethnicity/tribe), lifestyle and social factors (e.g., cigarette smoking, alcohol consumption, physical activity, education, occupation, income), family history of PCa, personal medical history of chronic diseases and history of PCa screening. PCa cases were also queried about signs and symptoms of PCa and any cancer treatment that they had received. Both cases and controls provided consent for the team to access their medical records to abstract clinical information relevant to PCa diagnosis and pathological features, comorbid conditions, and hospitalizations.

Body size measurements

At the clinic visit immediately following recruitment, trained study personnel took anthropometric measurements from each participant. Height (cm), weight (kg), waist (cm) and hip (cm) circumferences were measured using a stadiometer, beam scale, and non-stretching measuring tape, respectively, using standardized protocols. Body mass index (BMI) was calculated as weight (kg) divided by height in meters squared (kg/m^2). Waist-to-hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm). Waist-to-height ratio (WHtR) was calculated as waist circumference (cm) divided by height (cm). The data coordinating center at DFCI implemented quality control measures and data harmonization across centers [25].

Statistical Analysis

We compared characteristics between PCa cases and controls using Student t-tests or Wilcoxon rank-sum tests for normally or not-normally distributed continuous variables, and Chi-square tests for categorical variables; all tests were 2-sided using significance level $\alpha = 0.05$. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between anthropometric measurements and PCa risk [27]. We used normal probability plots and Q–Q plots to visualize data, and Kolmogorov–Smirnov and Shapiro–Francia tests to evaluate normality assumptions. The BMI was normally distributed; however, WC, WHR and WHtR were not normally distributed, and therefore were analyzed as categorical variables, using either center-specific quartiles based on the distributions among controls, or, when available, standard/clinically meaningful cutoff points. We used the WHO definitions of general obesity as BMI ≥ 30 kg/m^2, and central obesity as WC > 95 cm, WHR > 0.9 and WHtR > 0.59, although the cutoff points for WHR were further modified based on empirical distribution of data and literature [28–32]. Each anthropometric variable was fitted separately in each logistic regression model. Models were adjusted for the following categorical variables: participating hospital center in SSA, age at enrollment (5-year categories), occupation, cigarette smoking status (i.e., never, former, and current smoker), presence of hypertension and diabetes (see Table 1 for categories). Each of these variables satisfied the criteria for confounding because they changed the ORs between body size measurements and PCa by 10% or more. Education, alcohol drinking habits, and moderate physical activity did not change the ORs by 10% or more; therefore, they were not included as confounders in our final models. To evaluate the linear trend of PCa risk with increasing values or quartiles of body size measurements, we performed both the Cochran–Armitage and Wald tests (we present the Wald test p values from multivariate logistic regression models) [33].

We excluded 82 (3.7%) cases and 62 (3.1%) controls with missing anthropometric measures from the analysis. In addition, we excluded 17 (2.3%) controls with PSA ≥ 20 ng/ml because of the possibility that their higher PSA levels might have been due to undiagnosed PCa, and not from other comorbidities such as benign prostatic hyperplasia (BPH) or prostatic inflammation. We also carried out a sensitivity analysis where we excluded controls with a serum PSA > 4 ng/ml (to be consistent with the recommended guidelines for PSA screening cut-point used in the US). The proportion of missing data was $< 10\%$ (median 4–5%) for most variables; cases had slightly more missing data on anthropometric measures and some other variables (e.g., cigarette smoking, occupation) compared to controls (see Table 1).

Clinical variables and PCa risk categories We grouped PCa cases based on biopsy Gleason score (GS): ≤ 6, 7(3 + 4), 7 (4 + 3), 8–10, corresponding to the Grade Groups 1, 2, 3, ≥ 4. We also grouped PCa cases based on D'Amico risk classification scheme [34] using the following three categories: low-risk (i.e., T1–T2a, GS ≤ 6, and PSA ≤ 10 ng/ml), intermediate-risk (i.e., T2b, GS = 7, or PSA 10–20), and high-risk group (i.e., $\geq$ T2c, GS = 8–10, or PSA > 20).

Table 1 Selected characteristics of prostate cancer cases and controls from the Men of African Descent and Carcinoma of the Prostate (MADCaP) Consortium

Characteristics	Cases		Controls	
	$n = 2{,}200$		$n = 1{,}985$	
	n	%	*n*	%
Participating centers/hospitals				
Hôpital Général de Grand Yoff, Dakar, Senegal	232	10.5	226	11.4
37 Military Hospital, Accra, Ghana	184	8.4	187	9.4
Korle-Bu Teaching Hospital, Accra, Ghana	403	18.3	386	19.4
University College Hospital, Ibadan, Nigeria	201	9.1	123	6.2
University of Abuja Teaching Hospital, Abuja, Nigeria	98	4.5	104	5.2
Stellenbosch University, Cape Town, South Africa	170	7.7	139	7.0
WITS Health Consortium, Johannesburg, South Africa	912	41.5	820	41.3
African region[a]				
West Africa	1,118	50.8	1,026	51.7
South Africa	1,082	49.2	959	48.3
Age at enrollment (years)				
< 60	330	15.0	491	24.7
60–69	943	42.9	866	43.6
70–79	764	34.7	506	25.5
≥ 80	163	7.4	122	6.1
Marital status				
Single/never married	76	3.5	139	7.0
Married	1,632	74.2	1,494	75.3
Divorced or separated	152	6.9	139	7.0
Widowed	195	8.9	151	7.6
Missing	145	6.6	62	3.1
Education				
No formal education or < 4 years of schooling	349	15.9	329	16.6
5–12 years of schooling	696	31.6	499	25.1
Some secondary or Senior secondary schooling	486	22.1	722	36.4
Post-high school training	98	4.5	88	4.4
Some college	105	4.8	89	4.5
College graduate or postgraduate	297	13.5	159	8.0
Other	23	1.0	38	1.9
Missing	146	6.6	61	3.1
Smoking status				
Non-smokers	1,024	46.5	973	49.0
Former smokers	737	33.5	640	32.2
Current smokers	253	11.5	297	15.0
Missing	186	8.5	75	3.8
Alcohol drinking status				
Non-drinker	714	32.5	682	34.4
Former drinker	799	36.3	663	33.4
Current drinker	498	22.6	564	28.4
Missing	189	8.6	76	3.8
Occupation				
Professional	252	11.5	153	7.7
Managerial	154	7.0	106	5.3
Technical/sales/administrative/office worker	227	10.3	328	16.5
Service	190	8.6	240	12.1
Operators, fabricators and laborers	560	25.5	520	26.2
Farmer	69	3.1	78	3.9

Table 1 (continued)

Characteristics	Cases		Controls	
	n = 2,200		*n* = 1,985	
	n	%	*n*	%
Artisan	158	7.2	128	6.4
Other occupations[b]	439	20.0	364	18.3
Missing	151	6.9	68	3.4
Diabetes[c]				
No	1,794	81.5	1,615	81.4
Yes	287	13.0	318	16.0
Missing	119	5.4	52	2.6
Hypertension[c]				
No	1,059	48.1	1,112	56.0
Yes	1,022	46.5	821	41.4
Missing	119	5.4	52	2.6
Hypercholesterolemia (high blood cholesterol)[c]				
No	1,934	87.9	1,851	93.3
Yes	147	6.7	82	4.1
Missing	119	5.4	52	2.6
Number of comorbid conditions[c,d]				
0	834	37.9	790	39.8
1–2	1,080	49.1	997	50.2
≥ 3	286	13.0	198	10.0
First-degree relatives with prostate cancer[e]				
0	1,795	89.4	1,755	95.0
1	160	8.0	54	2.9
≥ 2	32	1.6	8	0.4
Missing	21	1	31	1.7
Moderate-intensity physical activity[f]				
No	1,819	82.7	1,606	80.9
Yes	194	8.8	301	15.2
Missing	187	8.5	78	3.9
Serum PSA at PCa diagnosis (cases) or at time of recruitment (controls) (ng/ml)[g]			n = 704	
0–3.9	11	0.5	599	85.1
4–9.9	252	11.5	68	9.7
10–19.9	341	15.5	20	2.8
20–49.9	455	20.7	11	1.6
≥ 50	993	45.1	6	0.9
Missing	148	6.7		
Clinical tumor stage[h]				
cT1	653	29.7		
cT2	809	36.8		
cT3	212	9.6		
cT4	157	7.1		
Missing/unknown	369	16.8		
Gleason score/grade group (GG)				
≤ 6/GG 1	363	16.5		
7(3 + 4)/GG 2	506	23.0		
7(4 + 3)/GG 3	385	17.5		
8–10/GG 4 or 5	789	35.9		
Missing	157	7.1		

Table 1 (continued)

Characteristics	Cases		Controls	
	n = 2,200		*n* = 1,985	
	n	%	*n*	%
D'Amico risk classification group[i]				
Low risk (T1–T2a and GS ≤ 6 and PSA ≤ 10)	74	3.4		
Intermediate risk (T2b, or GS = 7, or PSA 10–20)	393	17.9		
High risk (≥ T2c, or GS ≥ 8, or PSA > 20)	1,608	73.1		
Missing	125	5.6		

[a]West Africa: Hôpital Général de Grand Yoff, Senegal; 37 Military Hospital, Ghana; Korle-Bu Hospital, Ghana; University College Hospital, Nigeria; University of Abuja Teaching Hospital, Nigeria, South Africa: Stellenbosch University and Wits Health Consortium

[b]The distribution of other occupations among 439 cases and 364 controls is as follows: 10.3% and 11.3% were businesses, sales or trade; 9.6% and 8.5% were drivers, 4.1% and 4.7% were security, and 1.8% and 1.9% were pastors, respectively

[c]Based on information extracted from medical records of cases and controls

[d]Comorbidity score is calculated from the sum of 19 diseases for each participant. These diseases include: high blood pressure, malaria, diabetes, high blood cholesterol, rheumatoid arthritis, HIV/AIDS, ulcers, asthma, heart attack, chronic back pain, urinary tract infection, chronic bronchitis, hepatitis, thyroid disease, depression/anxiety, cirrhosis, syphilis, gonorrhea, and herpes. This information was extracted from medical records of participants

[e]First-degree relatives include blood-related father, brothers and/or sons of men who were not adopted: 2,008 cases and 1,848 controls

[f]Defined as moderate-intensity sports, fitness or recreational (leisure) activities that can cause small to moderate increase in breathing or heart rate such as brisk walking, cycling. This information was collected via self-reported questionnaire

[g]PSA in controls is reported only among 704 men who had laboratory serum PSA levels recorded in their medical records

[h]Clinical Stages: cT1 (T1, T1a, T1b, or T1c), cT2 (T2, T2a, T2b, or T2c), cT3 (T3, T3a, T3b, or T3c), and cT4 (T4)

[i]D'Amico Risk Category: low-risk (T1–T2a and GS ≤ 6 and PSA ≤ 10 ng/ml), intermediate-risk (T2b, or GS = 7, or PSA 10–20 ng/ml), and high-risk (≥ T2c, or GS ≥ 8, or PSA > 20 ng/ml)

About 7% of all PCa patients did not have clinical data on Gleason score or diagnostic PSA; however, a larger proportion (17%) had missing or unknown clinical tumor stage. We excluded 125 cases (5.7%) from D'Amico risk classification analyses because they had missing data on all three clinical parameters. We used polytomous logistic regression [35] to examine associations between anthropometric measures of overall and central obesity and PCa risk stratified by Gleason score/Grade group or D'Amico PCa risk levels as described above. These models were adjusted for the same confounders as the main analysis of total PCa risk.

Stratified analyses We also carried out several stratified analyses by African region (i.e., West vs. South Africa), and by presence or absence of diabetes, hypertension, heart attack or hypercholesterolemia or by the number of comorbid conditions (e.g., 0, 1–2, and 3+), which were abstracted from medical records of all PCa cases and controls to examine whether associations between body size measurements and PCa risk varied across different strata. To test for effect modification, we included interaction terms between each anthropometric measure and stratification covariates in separate logistic regression models containing the main effects; we used likelihood ratio tests to evaluate the statistical significance of the interaction terms [33]. All analyses were performed using R (v3.6.0) and Stata (StataCorp version 16).

Results

A total of 2,200 PCa cases and 1,985 controls were included in our analyses (Table 1). About 51% of PCa cases and controls were recruited in West Africa and 49% in South Africa. Most PCa cases (95%) were recruited from urology clinics. The majority of controls were recruited from departments of ophthalmology (40%), internal medicine (25%) or family medicine (7%), and general/orthopedic surgery (16%). Relative to controls, cases were slightly older (although the distributions of their 5-year age category were similar within each participating hospital, in concordance with the matching algorithm), were slightly more educated, and were more

likely to have worked in professional or managerial occupations. In comparison to controls, PCa cases were less likely to be current smokers (11.5% vs. 15%) or current alcohol drinkers (22.6% vs. 28.4%). Relative to controls, PCa cases were three times more likely to have a first-degree family history of PCa (9.6% vs. 3.3%), slightly more likely to have hypertension (46.1% vs. 41.4%) or three or more comorbidities (13% vs 10%), but less likely to have diabetes (13% vs 16%). Among PCa cases the distribution of Gleason score (GS) was as follows: 16.5% had GS ≤ 6, 23% GS: 7 (3 + 4), 17.5% GS: 7 (4 + 3), and 35.9% had GS of 8–10 (Table 1). The majority (81%) of cases had very high serum PSA levels at PCa diagnosis: 15.5%, 20.7% and 45.1% had PSA of 10–19.9, 20–49.9, and ≥ 50 ng/ml, respectively. Based on the D'Amico risk classification algorithm, 3.4% and 17.9% of PCa cases were classified as low- or intermediate risk, while the majority (73.1%) of patients was high risk.

Among controls, 30.4% were overweight and 16.4% were obese (Fig. 1). The prevalence of central obesity was very high; 90% and 70% of controls had WHR > 0.90, and WHtR > 0.50, respectively. Overall obesity and central obesity measures were more common in South than in West Africa (Fig. 1). The prevalence of overall and central obesity measures varied among controls recruited in different hospital departments, although their age distribution was similar (see Supplemental Table S1). The prevalence of overall obesity (BMI ≥ 30) was the highest among controls from ophthalmology (20%), followed by those from internal (17%) and family medicine (15%), but was the lowest among controls from general surgery (8%). However, the patterns of central obesity were not clearly associated with the department of control recruitment; some measures (e.g., WC and WHtR) were higher in controls recruited from internal medicine and ophthalmology, whereas WHR was higher in controls from family medicine.

Cases with aggressive PCa had lower body weight/BMI compared to controls or to cases with early-stage/low-grade PCa, suggesting weight loss related to cancer. For instance, the prevalence of general and central obesity decreased from 25% to 13.5%, and from 41.6% to 24.1%, respectively, with increasing D'Amico PCa risk classification from intermediate to high risk. In addition, 22.6% of PCa cases and 17.6% of controls reported having lost 5 kg or more in the past five years before recruitment ($p < 0.001$). A higher proportion of cases with more aggressive PCa pathological features: i.e. GS 8–10 (25.4%), stage CT4 (29%) or those with high-risk PCa (24%) reported the highest weight loss in comparison to patients with low-risk (11.8%) or intermediate-risk PCa (15.5%; $p < 0.001$). Most body size measurements were moderately correlated with age and one another; however, the correlations with WHtR were generally weaker compared to correlations with other anthropometric factors (see Supplemental Table S2).

Table 2 shows the associations of overall and central obesity measures with risk of total PCa. Overall obesity (BMI ≥ 30), and WC or WHtR were not associated with total PCa risk. However, men in the intermediate and highest category of WHR had ORs of 0.77 (95% CI 0.66–0.90) and 0.68 (95% CI 0.56–0.83), respectively, for total PCa compared to men in the lowest category (p trend < 0.001). Although the prevalence of general and central obesity was higher in South Africa, the patterns of associations between body size measurements and total PCa risk were similar between West and South Africa (Table 2). To address the issue of undiagnosed PCa among controls, we carried out a sensitivity analysis in which we excluded 105 controls with

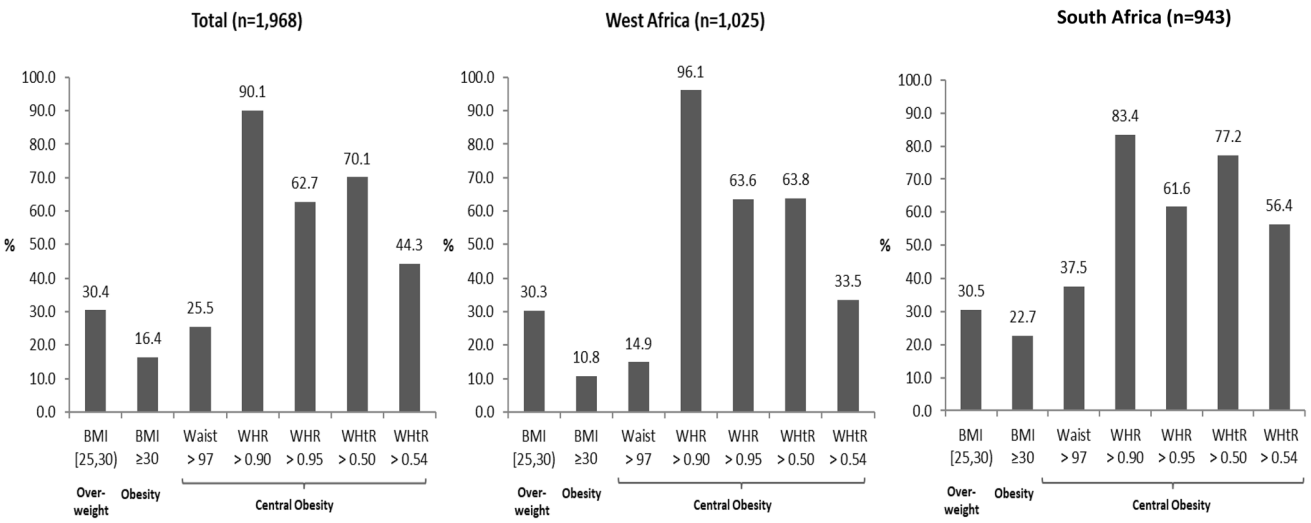

Fig. 1 Prevalence of overall obesity (BMI ≥ 30 kg/m^2) and central obesity measures among all controls, as well as stratified by geographic region. Abbreviation: *BMI* body mass index, *WHR* waist-to-hip ratio, *WHtR* waits-to-height ratio

Table 2 Body size measurements and risk of total prostate cancer among all participating centers and stratified by geographic region (West vs. South Africa)

Body size measurements	All Centers[a,b]						West Africa[b,c,d]						South Africa[b,e,f]					
	Controls		Cases		OR	95% CI	Controls		Cases		OR	95% CI	Controls		Cases		OR	95% CI
	n	%	*n*	%			*n*	%	*n*	%			*n*	%	*n*	%		
BMI (kg/m^2)																		
< 18.5	109	5.9	121	6.5	1.03	0.77–1.36	57	5.7	85	8.5	1.30	0.90–1.88	52	6.0	36	4.2	0.78	0.49–1.25
18.5–24.9	879	47.3	920	49.3	1.00	Ref	529	53.1	572	57.1	1.00	Ref	350	40.6	348	40.2	1.00	Ref
25–29.9	563	30.3	532	28.5	0.88	0.75–1.03	301	30.2	253	25.2	0.80	0.65–1.00	262	30.4	279	32.3	1.01	0.79–1.28
≥ 30	308	16.6	294	15.7	0.88	0.72–1.08	109	10.9	92	9.2	0.83	0.60–1.15	199	23.1	202	23.4	0.94	0.72–1.23
p for trend[g]					0.11						0.07						0.73	
Waist circumference (WC, cm)[h]																		
≤ 82.5	450	24.2	409	21.8	1.00	Ref	284	28.4	258	25.5	1.00	Ref	166	19.3	151	17.5	1.00	Ref
82.6–90.0	481	25.8	539	28.7	1.19	0.98–1.43	296	29.6	355	35.1	1.29	1.02–1.64	185	21.5	184	21.3	0.94	0.69–1.3
90.1–97.0	456	24.5	422	22.5	0.95	0.78–1.16	269	26.9	233	23.1	0.92	0.71–1.19	187	21.7	189	21.8	0.92	0.67–1.27
97.1–158	475	25.5	505	26.9	1.10	0.90–1.34	151	15.1	164	16.2	1.18	0.88–1.58	324	37.6	341	39.4	0.96	0.71–1.3
p for trend					0.90						0.92						0.86	
Waist-to-hip ratio (WHR)																		
≤ 0.95	695	37.4	798	43.2	1.00	Ref	363	36.3	410	40.8	1.00	Ref	332	38.6	388	46.1	1.00	Ref
0.96–0.99	774	41.6	716	38.8	0.77	0.66–0.90	478	47.8	443	44.0	0.79	0.64–0.97	296	34.4	273	32.5	0.75	0.60–0.95
≥ 1	391	21.0	333	18.0	0.68	0.56–0.83	158	15.8	153	15.2	0.80	0.59–1.09	233	27.1	180	21.4	0.60	0.46–0.77
p for trend					< 0.001						0.06						< 0.001	
Waist-to-height ratio (WHtR)																		
≤ 0.54	1032	55.6	1003	53.7	1.00	Ref	658	66.1	656	65.4	1.00	Ref	374	43.4	347	40.2	1.00	Ref
0.55–0.59	433	23.3	435	23.3	0.98	0.83–1.16	218	21.9	212	21.1	0.94	0.75–1.18	215	25.0	223	25.8	1.00	0.77–1.28
> 0.59	392	21.1	429	23.0	1.07	0.89–1.28	120	12.0	135	13.5	1.11	0.84–1.48	272	31.6	294	34.0	1.04	0.82–1.33
p for trend					0.50						0.60						0.74	

[a]Adjusted for seven hospital centers in West and South Africa, age at enrollment (5-year age category), occupational categories, smoking status (i.e., never, former, current), hypertension (yes vs no), and diabetes (yes vs. no)

[b]Controls with PSA ≥ 20 ng/ml and participants with missing values on anthropometric factors or covariates were not included

[c]Adjusted for five centers in West Africa, age at enrollment, occupation, smoking status, hypertension, and diabetes

[d]West Africa: Hôpital Général de Grand Yoff, Senegal; 37 Military Hospital, Ghana; Korle-Bu Hospital, Ghana; University College Hospital, Nigeria; University of Abuja Teaching Hospital, Nigeria

[e]Adjusted for two centers in South Africa, age at enrollment, occupation, smoking status, hypertension, and diabetes

[f]South Africa: Stellenbosch University and Wits Health Consortium

[g]Body mass index (BMI) < 18.5 kg/m^2 was excluded from the p for trend analysis

[h]Cutoff points for WC were based on the quartile distribution among controls

serum PSA > 4 ng/ml. Results of this sensitivity analysis were similar to those of the main analysis (see Supplemental Table S3).

Given that overall and central obesity are associated with other cardio-metabolic factors, we also conducted several stratified analyses by presence or absence of diabetes, either hypertension, heart attack or hypercholesterolemia, or by the number of comorbid conditions (e.g., 0, 1–2, 3+; see Supplemental Table S4). Although, in general, patterns of associations of body size measures with total PCa risk were similar, overall obesity (BMI ≥ 30) was inversely associated with PCa risk only among men without hypertension, heart attack or high cholesterol (OR = 0.62; 95% CI 0.44–0.88), or among those without any comorbidities (OR = 0.65; 95% CI 0.45–0.94), but not among men with these comorbidities (Supplemental Table S4). Interestingly, among men with three or more comorbidities, overall obesity was associated with a twofold higher risk of PCa (OR = 2.18; 95% CI 1.18–4.03, *p* trend = 0.02), as was the highest category of WHtR (OR= 2.10; 95% CI 1.19–3.70, *p* trend = 0.01). Nevertheless, the 95% CI overlapped for most of the stratified analyses, and therefore results were not statistically significantly different across various strata.

Table 3 shows the associations of body size measurements with risk of PCa stratified by Gleason score (GS) among all participating centers. Although, general obesity/BMI was not associated with low-grade PCa (GS ≤ 6), the highest categories of WC and WHtR were positive associated with modest increased risk of GS ≤ 6. With regard to GS 7 = 3 + 4 PCa, both general obesity (OR= 1.23; 95% CI: 0.91–1.68), and the highest categories of WC (OR= 1.48; 95% CI: 1.06–2.05), and WHtR (OR = 1.44; 95% CI: 1.09–1.90) were positively associated with risk of cancer (Table 3). By contrast, the associations of general and central obesity measures, except for WHR, with GS 7 = 4 + 3 prostate tumors were inverse or null. Overall obesity (OR= 0.70, 95% CI 0.53–0.92), and the highest categories of WHR (OR= 0.66, 95% CI 0.51–0.86), and WHtR (OR = 0.78, 95% CI 0.61–1.00) were also inversely associated with high-grade PCa (i.e., GS 8–10). There was consistent inverse association

Table 3 Body size measurements and risk of prostate cancer stratified by Gleason score/grade group (GG) among all participating centers

Body size measurements	Controls	Gleason score < 6/GG 1			Gleason score 7 (3 + 4)/GG 2			Gleason score 7 (4 + 3)/GG 3			Gleason score 8–10/GG 4 or 5		
		Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI
BMI (kg/m^2)													
< 18.5	109	21	1.03	0.61–1.73	27	1.14	0.72–1.82	15	0.68	0.38–1.21	55	1.11	0.78–1.60
18.5–24.9	879	159	1.00	Ref	191	1.00	Ref	174	1.00	Ref	377	1.00	Ref
25–29.9	563	103	1.02	0.77–1.36	141	1.12	0.87–1.45	100	0.87	0.65–1.15	176	0.71	0.57–0.89
≥ 30	308	51	1.07	0.74–1.56	93	1.23	0.91–1.68	52	0.77	0.53–1.11	96	0.70	0.53–0.92
p for trend			0.75			0.23			0.16			< 0.001	
Waist circumference (WC, cm)[c]													
≤ 82.5	450	65	1.00	Ref	81	1.00	Ref	66	1.00	Ref	187	1.00	Ref
82.6–90.0	481	98	1.37	0.96–1.95	109	1.13	0.82–1.57	102	1.31	0.93–1.86	217	1.07	0.84–1.37
90.1–97.0	456	87	1.26	0.87–1.81	107	1.16	0.83–1.61	76	0.99	0.69–1.44	144	0.72	0.55–0.94
97.1–158	475	84	1.54	1.05–2.25	156	1.48	1.06–2.05	97	1.14	0.78–1.65	163	0.78	0.59–1.02
p for trend			0.06			0.02			0.96			0.01	
Waist-to-hip ratio (WHR)													
≤ 0.95	695	137	1.00	Ref	181	1.00	Ref	147	1.00	Ref	317	1.00	Ref
0.96–0.99	774	143	0.88	0.67–1.17	167	0.81	0.63–1.04	127	0.72	0.55–0.95	264	0.74	0.60–0.91
≥ 1	391	51	0.69	0.47–1.01	94	0.81	0.60–1.10	61	0.57	0.40–0.81	123	0.66	0.51–0.86
p for trend			0.07			0.12			0.001			0.001	
Waist-to-height ratio (WHtR)													
≤ 0.54	1,032	175	1.00	Ref	209	1.00	Ref	178	1.00	Ref	416	1.00	Ref
0.54–0.59	433	86	1.28	0.95–1.73	108	1.11	0.85–1.47	81	0.99	0.73–1.34	153	0.80	0.64–1.01
> 0.59	392	72	1.47	1.05–2.05	135	1.44	1.09–1.90	82	1.04	0.75–1.43	136	0.78	0.61–1.00
p for trend			0.02			0.01			0.84			0.03	

[a]Adjusted for seven hospital centers in West and South Africa, age at enrollment (5-year groups), occupation, smoking status, hypertension and diabetes

[b]Controls with PSA ≥ 20 ng/ml and all participants with missing values were excluded;

[c]Cutoff points were based on the quartile distribution among controls

Table 4 Body size measurements and risk of prostate cancer stratified by Gleason score/grade group (GG) in West Africa

Body size measurements	Controls	Gleason score < 6/GG 1			Gleason score 7 (3 + 4)/GG 2			Gleason score 7 (4 + 3)/GG 3			Gleason score 8–10/GG 4 or 5		
		Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI
BMI (kg/m^2)													
< 18.5	57	18	1.22	0.67–2.22	18	1.44	0.79–2.62	12	1.11	0.56–2.2	35	1.29	0.81–2.07
18.5–24.9	529	122	1.00	Ref	111	1.00	Ref	100	1.00	Ref	228	1.00	Ref
25–29.9	301	79	1.15	0.82–1.61	55	0.99	0.68–1.44	36	0.74	0.48–1.14	82	0.65	0.48–0.89
≥ 30	109	26	0.98	0.59–1.62	19	0.94	0.53–1.64	9	0.55	0.26–1.17	37	0.81	0.52–1.24
p for trend			0.78			0.76			0.08			0.06	
Waist circumference (WC, cm)[c]													
≤ 82.5	284	51	1.00	Ref	48	1.00	Ref	38	1.00	Ref	114	1.00	Ref
82.6–90.0	296	77	1.39	0.92–2.09	65	1.20	0.78–1.84	61	1.48	0.94–2.35	146	1.27	0.93–1.73
90.1–97.0	269	67	1.26	0.83–1.92	51	1.10	0.70–1.73	36	0.97	0.58–1.62	77	0.73	0.51–1.03
97.1–158	151	51	1.76	1.11–2.79	40	1.60	0.97–2.62	22	1.20	0.66–2.17	51	0.84	0.56–1.27
p for trend			0.04			0.12			0.98			0.07	
Waist-to-hip ratio (WHR)													
≤ 0.95	363	99	1.00	Ref	73	1.00	Ref	66	1.00	Ref	165	1.00	Ref
0.96–0.99	478	110	0.88	0.62–1.23	99	1.03	0.71–1.48	64	0.60	0.39–0.91	164	0.77	0.58–1.02
≥ 1	158	36	0.73	0.44–1.20	32	0.99	0.57–1.72	27	0.64	0.34–1.18	56	0.76	0.50–1.14
p for trend			0.21			0.98			0.07			0.09	
Waist-to-height ratio (WHtR)													
≤ 0.54	658	142	1.00	Ref	129	1.00	Ref	106	1.00	Ref	266	1.00	Ref
0.54–0.59	218	64	1.31	0.92–1.87	42	0.96	0.64–1.44	31	0.90	0.57–1.42	74	0.80	0.59–1.10
> 0.59	120	39	1.47	0.95–2.28	32	1.47	0.92–2.36	20	1.24	0.71–2.16	43	0.81	0.54–1.21
p for trend			0.05			0.19			0.65			0.16	

West Africa: Hôpital Général de Grand Yoff, Senegal; 37 Military Hospital, Ghana; Korle-Bu Hospital, Ghana; University College Hospital,Nigeria; University of Abuja Teaching Hospital, Nigeria

[a]Adjusted for five hospital centers in West Africa, age at enrollment (5-year category), occupation, smoking status, hypertension and diabetes

[b]Controls with PSA ≥ 20 ng/ml and participants with missing values were excluded

[c]Cutoff points were based on the quartile distribution among controls

of WHR with risk of PCa across all Gleason score, with the highest category (WHR ≥ 1) showing statistically significant ORs of 0.57–0.81 across GS categories. Patterns of associations between anthropometric factors and PCa risk stratified by Gleason score were generally similar between West Africa (Table 4) and South Africa (Table 5).

Overall and central obesity were also associated with D'Amico PCa risk groups (Tables 6, 7). Since only 74 cases (3.4%) were classified as low risk, associations for this group are not presented. The associations of overall obesity (OR = 1.38, 95% CI 0.99–1.93) and several central obesity measures: e.g., WC > 97 cm (OR = 1.60, 95% CI 1.10–2.33), or WHtR > 0.59 (OR = 1.68, 95% CI 1.24–2.29) with intermediate-risk PCa were consistently positive (Table 6). However, intermediate-risk PCa was inversely associated with WHR (OR = 0.56; 95% CI 0.39–0.80 when comparing WHR ≥ 1 vs. ≤ 0.95). Overall obesity (OR = 0.77, 95% CI 0.61–0.95), and the highest category of WHR (OR = 0.74, 95% CI 0.60–0.92) were also inversely associated high-risk PCa, but not with other measures of central obesity (WC or WHtR; Table 6). Although some associations of overall and central obesity with intermediate-risk PCa were stronger in West Africa compared to South Africa (Table 7), results were not statistically significantly different.

Discussion

In this large multi-center, hospital-based case–control study of urban African men, we found that half of the study subjects were overweight or obese, and 90% of them had central obesity as defined by WHR > 0.90. Despite evidence of higher weight loss (≥ 5 kg before recruitment) among PCa cases with more aggressive PCa (i.e., those with a GS 8–10 or D'Amico high-risk group), we found that several parameters of overall and central obesity were statistically

Table 5 Body size measurements and risk of prostate cancer stratified by Gleason score/grade group (GG) in South Africa

Body size measurements	Controls	Gleason score < 6/GG 1			Gleason score 7 (3 + 4)/GG 2			Gleason score 7 (4 + 3)/GG 3			Gleason score 8–10/GG 4 or 5		
		Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI	Cases	OR[a,b]	95% CI
BMI (kg/m^2)													
< 18.5	52	3	0.58	0.17–1.97	9	0.83	0.38–1.81	3	0.29	0.09–0.97	20	1.04	0.58–1.88
18.5–24.9	350	37	1.00	Ref	80	1.00	Ref	74	1.00	Ref	149	1.00	Ref
25–29.9	262	24	0.80	0.46–1.40	86	1.29	0.90–1.86	64	1.09	0.74–1.62	94	0.81	0.58–1.12
≥ 30	199	25	1.11	0.62–1.97	74	1.41	0.96–2.08	43	0.98	0.63–1.53	59	0.64	0.44–0.94
p for trend			0.81			0.07			0.99			0.02	
Waist circumference (WC, cm)[c]													
≤ 82.5	166	14	1.00	Ref	33	1.00	Ref	28	1.00	Ref	73	1.00	Ref
82.6–90.0	185	21	1.33	0.64–2.76	44	1.02	0.61–1.73	41	1.08	0.62–1.87	71	0.69	0.46–1.06
90.1–97.0	187	20	1.24	0.59–2.61	56	1.28	0.77–2.13	40	0.99	0.57–1.74	67	0.62	0.41–0.95
97.1–158	324	33	1.15	0.56–2.36	116	1.38	0.86–2.23	75	1.12	0.66–1.88	112	0.63	0.43–0.94
p for trend			0.89			0.10			0.73			0.04	
Waist-to-hip ratio (WHR)													
≤ 0.95	332	38	1.00	Ref	108	1.00	Ref	81	1.00	Ref	152	1.00	Ref
0.96–0.99	296	33	0.91	0.55–1.50	68	0.66	0.46–0.95	63	0.82	0.56–1.21	100	0.71	0.52–0.97
≥ 1	233	15	0.54	0.29–1.03	62	0.69	0.48–1.01	34	0.51	0.32–0.81	67	0.58	0.41–0.82
p for trend			0.08			0.04			0.01			< 0.001	
Waist-to-height ratio (WHtR)													
≤ 0.54	374	33	1.00	Ref	80	1.00	Ref	72	1.00	Ref	150	1.00	Ref
0.54–0.59	215	22	1.17	0.65–2.12	66	1.29	0.87–1.9	50	1.08	0.71–1.65	79	0.79	0.56–1.11
> 0.59	272	33	1.35	0.78–2.35	103	1.45	1.01–2.08	62	1.05	0.70–1.58	93	0.76	0.54–1.06
Wald test for trend			0.28			0.05			0.81			0.09	

South African centers included: Stellenbosch University and the Wits Health Consortium

[a]Adjusted for hospital centers in South Africa, age at enrollment (5-year group), occupation, smoking status, hypertension and diabetes

[b]Controls with PSA ≥ 20 ng/ml and all participants with missing values were excluded

[c]Cutoff points were based on the quartile distribution among controls

significantly associated with 23%–68% higher odds of GS 7 = 3 + 4 PCa or D'Amico intermediate-risk category, but there was no association with total PCa risk. Although the prevalence of general and central obesity were higher in South vs. West Africa in our data, which was similar to other reports [24], the associations between body size measures and risks of overall PCa and by Gleason score or D'Amico risk score did not differ much by African region.

The high prevalence of general obesity and several measures of central obesity in African men in our study (presented in Fig. 1) is concerning and underscores the importance of obesity prevention in Africa. However, to be noted is that our controls were urban men hospitalized for other conditions including hypertension and cardiovascular diseases, and therefore their prevalence of obesity (16%) might be higher compared to population-based controls or men in the rural areas [23, 36]. In 2016, the WHO reported that the prevalence of general obesity ranged from 2.5% to 6.6% in West Africa men, but was almost 31% in black South Africans [37]. Although the prevalence of obesity in African American men is reported to be over 41% [38], the average BMI among men in all African regions has increased steadily in the past 25 years [24].

Central obesity measurements were highly prevalent among controls (ranging from 44% to 90%), and were consistently high across all seven participating centers in West and South Africa. In recent years, the reported prevalence of central obesity has been alarmingly high in African countries. For example, in a study of Ghanaian adults aged 50 years or older, the prevalence of abdominal obesity among men was 54.4% [23]. Similarly, among South African men, the prevalence of central obesity has been reported to be between 36% and 54% [32]. Abdominal fat, especially visceral fat, is metabolically more active, and poses higher risk than other fat for many cancers, including PCa [14, 15], as well as other chronic conditions, including cardiovascular disease, hypertension, and diabetes. Reasons for the extremely high prevalence of abdominal obesity in urban

Table 6 Body size measurements and risk of prostate cancer according to D'Amico risk classification among all participating centers

Body size measurements	Controls	D'Amico Risk Group					
		Intermediate risk[a]			High risk[a]		
		Cases	OR[b]	95% CI	Cases	OR[b]	95% CI
BMI (kg/m^2)							
< 18.5	109	10	0.53	0.27–1.07	109	1.11	0.83–1.49
18.5–24.9	879	129	1.00	Ref	763	1.00	Ref
25–29.9	563	121	1.28	0.96–1.71	391	0.82	0.69–0.97
≥ 30	308	85	1.38	0.99–1.93	195	0.77	0.61–0.95
p for trend[h]			0.05			0.01	
Waist circumference (WC, cm)[c]							
≤ 82.5	450	55	1.00	Ref	343	1.00	Ref
82.6–90.0	481	70	1.04	0.7–1.54	456	1.21	0.99–1.47
90.1–97.0	456	76	1.13	0.76–1.67	327	0.90	0.73–1.11
97.1–158	475	144	1.60	1.10–2.33	341	0.98	0.78–1.22
p for trend			0.01			0.25	
Waist-to-hip ratio (WHR)							
≤ 0.95	695	153	1.00	Ref	615	1.00	Ref
0.96–0.99	774	122	0.79	0.60–1.04	567	0.77	0.66–0.91
≥ 1	391	58	0.56	0.39–0.80	269	0.74	0.60–0.92
p for trend			0.001			0.002	
Waist-to-height ratio (WHtR)							
≤ 0.54	1032	129	1.00	Ref	843	1.00	Ref
0.54–0.59	433	94	1.40	1.03–1.90	325	0.90	0.75–1.08
> 0.59	392	122	1.68	1.24–2.29	291	0.95	0.78–1.15
p for trend			< 0.001			0.40	

[a]D'Amico risk category: intermediate-risk (T2b, GS = 7, PSA 10–20) and high-risk (≥ T2c, GS 8–10, or PSA > 20); n = 74 cases with low-risk (T0–T2a and GS ≤ 6 and PSA ≤ 10) were excluded from stratification analysis

[b]Multinomial logistic regression models were adjusted for age at enrollment (5-year group), hospital centers, occupation, smoking status, hypertension, and diabetes

[c]Cutoff points were based on the quartile distribution among controls

African men might be related to genetics or increased westernization and lifestyle changes [24].

The relatively consistent associations of body size measures with intermediate-risk PCa suggest a potential link between general and central obesity with PCa in African men that warrants further investigation. The less consistent findings for low-risk and high-risk GS are not completely surprising. In this population with little PCa screening (relative to the US), very few cases had low-risk PCa (D'Amico low risk $n = 74$); thus, the analyses among low-risk group were underpowered. Analyses of the high-risk groups (GS of 8–10: $n = 778$, D'Amico high risk: $n = 1{,}590$) were not underpowered, but were likely to have been affected by the presence of cancer, exemplifying reverse causation. The prevalence of general obesity was twice as high among D'Amico intermediate-risk cases (25%) as among high-risk cases (13.5%). Moreover, a higher proportion of PCa cases with GS 8–10 (25.4%), advanced stage T4 cancer (29%) or those with high-risk PCa (24%) reported the highest weight loss in comparison to low-risk cases (11.8%) or to PCa patients with intermediate-risk (15.5%; $p < 0.001$), suggesting weight loss/cachexia related to cancer progression (duration of PCa) that is consistent with reverse causation, rather than an effect of body weight/size on disease risk.

Although PCa is the most common cancer in men in most African countries, and obesity rates are rising in Africa [23, 24], few studies of body size and PCa risk have focused on African or Afro-Caribbean men. A recently published study in Ghana, which included 566 PCa cases and 964 controls reported a 1.9-fold increased risk of PCa (95% CI 1.1–3.1) among men associated with general obesity and a 1.8-fold increased risk associated with larger waist circumference (95% CI 1.2–2.5) [39]. In this study, most cases (87%) were recruited from the Korle-Bu Teaching Hospital in Ghana (one of the centers of this MADCaP consortium study; although none of the cases reported in that earlier study were included in the present analyses), but the controls were drawn from a population-based sample of 1,037

Table 7 Body size measurements and risk of prostate cancer according to D'Amico risk classification stratified by geographic region (West vs. South Africa)

Body size measurements	West Africa							South Africa						
	Controls	D'Amico intermediate risk[a]			D'Amico high risk[a]			Controls	D'Amico intermediate risk[a]			D'Amico high risk[a]		
		Cases	OR[b]	95% CI	Cases	OR[b]	95% CI		Cases	OR[b]	95% CI	Cases	OR[b]	95% CI
BMI (kg/m^2)														
< 18.5	57	2	0.37	0.08–1.64	82	1.38	0.95 – 2.00	52	8	0.64	0.29–1.43	27	0.85	0.50–1.43
18.5–24.9	529	44	1.00	ref	514	1.00	ref	350	85	1.00	ref	249	1.00	ref
25–29.9	301	31	1.28	0.77–2.12	213	0.77	0.61–0.96	262	90	1.28	0.90–1.83	178	0.92	0.70–1.21
≥ 30	109	13	1.66	0.81–3.40	76	0.78	0.56–1.09	199	72	1.36	0.93–2.00	119	0.78	0.57–1.06
p for trend[h]			0.16			0.03				0.10			0.12	
Waist circumference (WC, cm)c														
≤ 82.5	284	19	1.00	ref	236	1.00	ref	166	36	1.00	ref	107	1.00	ref
82.6–90.0	296	21	0.93	0.47–1.81	327	1.33	1.04–1.70	185	49	1.05	0.64–1.73	129	0.90	0.63–1.28
90.1–97.0	269	18	0.84	0.42–1.69	203	0.89	0.69–1.17	187	58	1.22	0.75–2.00	124	0.81	0.56–1.16
97.1–158	151	32	2.71	1.41–5.21	127	1.03	0.76–1.41	324	112	1.31	0.82–2.07	214	0.85	0.61–1.19
p for trend			0.01			0.46				0.18			0.33	
Waist-to-hip ratio (WHR)														
≤ 0.95	363	36	1.00	ref	362	1.00	ref	332	117	1.00	ref	253	1.00	ref
0.96–0.99	478	42	1.05	0.63–1.76	388	0.78	0.62–0.97	296	80	0.74	0.53–1.03	179	0.76	0.59–0.99
≥ 1	158	12	1.09	0.48–2.50	139	0.81	0.59–1.12	233	46	0.49	0.33–0.72	130	0.67	0.50–0.90
p for trend			0.80			0.08				< 0.001			0.01	
Waist-to-height ratio (WHtR)														
≤ 0.54	658	42	1.00	ref	598	1.00	ref	374	87	1.00	ref	245	1.00	ref
0.54–0.59	218	24	1.58	0.91–2.75	179	0.88	0.69–1.12	215	70	1.28	0.88–1.87	146	0.90	0.68–1.20
> 0.59	120	24	3.38	1.85–6.17	109	1.00	0.74–1.35	272	98	1.36	0.95–1.95	182	0.91	0.69–1.20
p for trend			< 0.001			0.69				0.09			0.50	

[a]D'Amico category: intermediate-risk (T2b, GS = 7, PSA 10–20) and high-risk (≥ T2c, GS 8–10, or PSA > 20). *n* = 74 cases with low-risk (T0–T2a and GS ≤ 6 and PSA ≤ 10) were excluded from the stratification analysis

[b]Multinomial logistic regression models were adjusted for age at enrollment (5-year group), hospital centers in either West or South Africa, occupation, smoking status, hypertension, and diabetes

[c]Cutoff points were based on the quartile distribution among controls

men recruited for a PCa screening study [39]. In the earlier Ghana study, the prevalence of general obesity in the same catchment population was much lower (13% of cases and 9% of controls) than in the current study (43% of cases and 25% of controls), since the earlier study was conducted 16 years ago when obesity was emerging as a problem there. It is reassuring that in both the earlier and current studies in Ghana, the prevalence of general obesity in cases is higher than that in controls. In a separate study in Barbados, West Indies, several measures of central obesity were associated with increased risk of PCa: WHR ≥ 0.96 versus < 0.87 with OR = 2.11 (95% CI, 1.54–2.88) and waist size ≥ 99 cm with an OR = 1.84 (95% CI 1.19–2.85) [20].

The few studies that have evaluated the relationship of general obesity and PCa in African American men have yielded conflicting results [40–42]. A case–control study[40] among African American men in Maryland reported inverse associations between obesity (BMI > 30) and risks of non-aggressive (OR = 0.62) or aggressive PCa (OR= 0.41). The North Carolina/Louisiana prostate cancer (PCaP) project that included 991 African American cases reported no association between obesity and aggressive PCa (OR = 1.09; 95% CI 0.71, 1.67), although the comparison group in this study were non-aggressive PCa cases, and not controls [43]. Similarly, the Multiethnic Cohort Study, which included 9,284 African American men, reported no association between obesity and overall PCa risk (RR = 1.05, 95%CI 0.81–1.36 for BMI ≥ 35 vs. < 25 kg/m^2)[44]. By contrast, among African American men who participated in the SELECT trial[41], BMI was positively associated with total PCa risk [BMI ≥ 35 vs. < 25 kg/m^2: hazard ratio (HR) 1.49; 95% CI 0.95–2.34, p for trend = 0.03].

Our study has several strengths. It is the first to examine associations of body size measurements with risks of total and aggressive PCa in African men, with a large sample size and patients recruited from seven clinical centers in four countries in West and South Africa. The study used standardized protocols across all participating centers collecting high-quality detailed information on demographic, social and lifestyle factors, as well as anthropometric measures, and abstracted relevant clinical information on PCa and comorbidities from medical records. Only a small percentage of data (median of 5%) were missing. Anthropometric factors were measured during in-person interviews of both cases and controls. However, although the procedures were standardized across centers, and the field teams used the same protocols for all patients, body size and shape at diagnosis could have been affected by cachexia, among PCa patients with advanced stage or high-grade cancer. Selection and referral bias are also possible, because all clinical centers included in the study were tertiary-care hospitals. However, since most cancers are treated in tertiary hospital centers and controls were selected from the same hospitals, differential selection bias was probably minimal. Since PSA screening is seldom used in Africa, all PCa cases were clinically diagnosed (not PSA screened), and all controls were also not screened via a serum PSA test. The use of hospital controls, who are usually more ill than population-based controls, might have also affected the direction or strength of the associations. To minimize this bias, we selected hospital controls primarily from departments with less apparently serious conditions, including Ophthalmology (40%), Internal and Family Medicine (32%), and Orthopedics (15%). It should be noted that some control subjects, especially those recruited in internal medicine, may have been hospitalized because of diabetes, hypertension, or other cardiovascular disease, related to higher BMI/obesity, which could potentially have affected our results. Although results of several stratified analyses did not reveal statistically significant differences in associations of body size measures with PCa risk across strata of comorbidities, some of the obesity-related conditions among controls could have potentially underestimated the ORs for those associations. As noted earlier, we used standardized procedures and protocols at all centers but had to make adjustments at each center based on the needs of clinical care locally. These variations may have had a slight impact on the completeness of tumor staging and grading of PCa patients. Finally, our results are not generalizable to African population living outside Africa, given differences in screening patterns, migration or changes in dietary patterns.

Conclusion

In conclusion, in this large multi-center case–control study of African men, we found that general obesity and several measures of central adiposity (e.g., waist size and WHtR) were positively associated with intermediate-risk PCa. Given the high prevalence of general and central obesity in our study population, and their rising prevalence in Africa, large cohort studies are needed to better clarify the role of obesity and PCa in various African populations. Our results support policies that target a potentially modifiable risk factor for many diseases including PCa, in order to improve public health in Africa.

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Author contributions IA, AOA, AWH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: IA, AWH, AOA, TRR, JSJ, TER. Data acquisition and management: All authors. Statistical analysis: WKL, IA, AWH. Interpretation of data: All authors. Drafting of manuscript: IA, WKL, JSZ, AOA, AWH, JSJ, TER. Critical revision of manuscript for important intellectual content: All authors. Supervision: IA, AWH, AOA, TRR.

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Data availability The data that support the findings of this study are available upon request from the corresponding authors or the Principal Investigator of the MADCaP Network. The data are not publicly available due to privacy or ethical restrictions. Requests for data access can be submitted via the MADCaP Network website at: https://www.madcapnetwork.org/.

Code availability R coding and Stata programs that were used for data analyses are available upon request from the corresponding authors.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol and procedures were approved by the Institutional Ethical Review Boards (IRBs) of all participating institutions.

Consent to participate All cases and controls provided written informed consent to participate in the study.

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