

High bone density is associated with prostate cancer in older Afro-Caribbean men: Tobago Prostate Survey

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Abstract

Objective To test the hypothesis that bone mineral density (BMD), a possible surrogate of lifetime exposure to hormone/growth factor/vitamin D/calcium exposure, is higher in prostate cancer cases than controls. **Methods** Hip BMD was measured by dual X-ray absorptiometry in 222 Afro-Caribbean screening-detected prostate cancer cases and 1,503 screened non-cases, aged 45–79, in the population-based Tobago Prostate Survey. Because possible skeletal metastases may modulate BMD, men with prostate specific antigen >20 ng/ml or highly undifferentiated tumors (Gleason score ≥8) were excluded. Mean BMD, adjusted for age and body mass index, was compared in cases and non-cases by analysis of variance. Risk across age group-specific BMD quartiles was compared using logistic regression.

Results Overall, adjusted mean hip BMD was higher in cases (1.157 g/cm²) than non-cases (1.134 g/cm²) ($p = 0.02$). In men aged 60–79, prostate cancer risk was two-fold higher (OR, 2.12; 95% CI: 1.21–3.71) in the highest BMD quartile compared to the lowest. There was no association in younger men (interaction, $p = 0.055$).

Conclusions High bone density is associated with prostate cancer among older men, consistent with an etiological role for lifetime exposure to factors which modulate bone density. However, other etiologies may dominate prostate cancer risk among younger men.

Keywords Afro-Caribbean · Bone mineral density · Hormones · Prostate cancer

Abbreviations

BMD	Bone mineral density
BMI	Body mass index
IGFI	Insulin-like growth factor I
OR	Odds ratio
PSA	Prostate specific antigen
ANOVA	Analysis of variance
NHANES	National Health and Nutrition Examination Survey
SD	Standard deviation
CI	Confidence interval

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Introduction

High prostate cancer incidence or prevalence has been reported in populations of African descent in the US [1], and on the Caribbean islands of Jamaica [2] and

Tobago [3], compared with Caucasian populations. Androgen metabolism has been suspected as a contributor to the elevated risk of prostate cancer in populations of African descent compared with Caucasians, but data directly supporting this hypothesis are sparse. Higher serum androgen levels have been observed in some [4, 5], but not all [6] studies of African Americans compared with whites. A number of studies of an androgen receptor CAG repeat polymorphism have documented a higher frequency of shorter CAG repeats in populations of African descent compared with Caucasians and other ethnic groups [7–10]. Studies have shown that a shorter CAG repeat tract is associated with higher androgen receptor activity in cell lines [11, 12] and in mouse models [13].

Circulating levels of insulin-like growth factor I (IGF1) have also been associated with prostate cancer risk in prospective [14, 15] and case-control [16] studies of predominantly Caucasian populations though results have not been consistent [17]. Significantly higher serum IGF-1 levels have been observed in Afro-Caribbean men, compared with similar aged Pakistani and European men [18]. Nevertheless, circulating levels of androgens and growth factors may not accurately reflect intra-prostatic concentrations and metabolism and thereby characterize a man's lifetime exposure to these mitogenic factors.

Bone mineral density (BMD) has been proposed as a surrogate measure of lifetime growth factor and endogenous sex hormone exposure [19, 20]. Bone contains functional receptors for IGF-1 [21] and sex steroid hormones [22] and is sensitive to IGFs and androgens [22, 23]. Moreover, BMD is considerably greater in men of African compared to Caucasian ancestry, and this skeletal difference has been attributed in part to ethnic differences in growth factor and sex steroid hormone production and/or sensitivity [24].

BMD has been positively associated with breast cancer risk [19] and prostate cancer risk in Caucasian populations [25], but these associations have not been examined in populations of African descent. Thus, we conducted the current study in a high risk Afro-Caribbean population residing on the island of Tobago. Age-specific screening-detected prostate cancer prevalence rates in the Tobago population are 3–4 times higher [3] than observed in a similarly screened US Caucasian population [26]. We tested the hypothesis that BMD, as a surrogate marker of lifetime sex hormone/growth factor exposure, would be higher in Afro-Caribbean men with screening-detected prostate cancer compared to men without prostate cancer: those with normal screening results (serum prostate specific antigen (PSA) <4 ng/ml and a normal digital rectal

exam) and no biopsy, and those with abnormal screening results and one or more biopsies which were negative for prostate cancer.

Methods

Population

The Tobago Prostate Survey is a population-based, longitudinal prostate cancer screening study which has been conducted on the Caribbean island of Tobago, Trinidad and Tobago, since late 1997. More than 60% of the male population, aged 40–79, has participated. The study was approved by the Institutional Review Board of the University of Pittsburgh, and the Institutional Review Board of the Division of Health and Social Services, Tobago House of Assembly. Written informed consent was obtained from each participant. The methods have been described in detail [3]. Briefly, men with abnormal screening results, serum PSA ≥ 4 ng/ml, or abnormal digital rectal exam other than simple enlargement, were referred for sextant biopsy by surgeons at the local regional hospital. Thirty-one percent of screened men were referred for biopsy. Ninety percent of men referred for biopsy underwent biopsy. PSA assays (Abbot AxSYM PSA assay, Abbott Laboratories, Abbott Park, IL, USA) and biopsy pathology were completed at the University of Pittsburgh Pathology Laboratory.

Bone mineral density

Bone mineral density measurements were begun in March 2000. Men enrolled prior to that time were contacted to return for a bone density measurement. Men enrolled after that time were scheduled for a bone density measurement around the time of their first visit. Total hip BMD was measured using a Hologic QDR 4500W densitometer (Hologic Inc., Bedford, MA). Densitometry staff were trained and certified by Hologic. Densitometry quality assurance and quality control were completed by SYNARC, Inc. (Maynard, MA). Longitudinal machine stability was assessed from plots of daily spine phantom scans, and reviewed monthly. A weekly printout of quality control plots was generated to detect short-term inconsistencies and long-term drift. Quality control scans were reviewed to ensure that the BMD and bone mineral content of the scanner were within normal limits. The coefficient of variation for BMD was 0.44%. Scan analysis quality was ensured by central review of scans. In addition, scans that appeared

unusual or difficult to analyze were flagged for review by SYNARC, Inc.

Data analysis

All men diagnosed with prostate cancer at baseline (prevalent cases) or at a second visit approximately two years after baseline (incident cases) were designated cases and were compared with screened men not diagnosed with prostate cancer (non-cases). No cases were observed in men younger than 45. Therefore, analyses were limited to men aged 45–79 with bone scan data (298 cases and 1,531 non-cases). Men of non-African ancestry were excluded from analyses (five cases, 10 non-cases). Bone metastases may modulate hip BMD. Since scintigraphy, the standard method for diagnosis of bone metastases, was not available on the island of Tobago, we excluded men most likely to be affected by skeletal metastases: those with highly undifferentiated tumors (Gleason scores 8, 9, 10) and/or high serum PSA values (PSA > 20 ng/ml). Excluded were 11 cases with Gleason \geq 8 and PSA > 20 ng/ml; 16 cases with Gleason \geq 8 and PSA \leq 20 ng/ml; 42 cases with Gleason < 8 and PSA > 20 ng/ml; 16 non-cases with PSA > 20 ng/ml. Men undergoing orchiectomy or medical androgen ablation prior to densitometry ($n = 2$) were also excluded from the analyses. Remaining for analysis were 222 cases and 1,503 non-cases. Anthropometric measurements and total hip BMD were compared between cases and non-cases using analysis of variance (ANOVA). Models were constructed to compare BMD by prostate cancer status, adjusted for age (continuous), for age and body mass index (BMI, weight in kilograms/height in meters squared), and for age, BMI, and the interaction between age and BMD by prostate cancer status. Further ANOVA models were constructed in younger (age 45–59) and older (60–79) age groups. Quartiles were assigned based on the distribution of hip BMD in the study population aged 45–59, or aged 60–79. Prostate cancer risk associated with quartiles of hip BMD was calculated by logistic regression adjusted for age (continuous) and BMI among younger and older men. Similar logistic regression models were constructed to estimate the prostate cancer risk associated with hip BMD as a continuous variable. All statistical tests were two-sided and were considered statistically significant if $p < 0.05$.

Results

Bone density and related covariates were analyzed in 222 cases (179 prevalent and 43 incident cases) and

1,503 non-cases. The Gleason scores 5, 6 and 7 were observed in 2, 151, and 69 men, respectively.

Among prostate cancer cases, bone density was measured prior to diagnosis (mean 0.9 years, SD 0.7, median 0.7, range 0.1–2.38 years) in 92 men. Bone density was measured after diagnosis (mean 0.8 years, s.d. 0.6, median 0.6, range 0–2.7 years) in 130 men.

Mean age in cases was 63.6 years compared with 56.8 years in non-cases (Table 1). Age-adjusted BMI was highly correlated with total fat mass ($r = 0.84$) and lean mass ($r = 0.70$) in both cases and non-cases ($r = 0.84$, $r = 0.75$, respectively, all $p < 0.001$). Age-adjusted BMI in cases was slightly higher than in non-cases, 27.6 kg/m² (95% CI 27.1–28.2) compared with 27.0 kg/m² (95% CI 26.8–27.2), $p = 0.055$. Age and BMI-adjusted hip BMD was higher in cases, 1.157 g/cm² (95% CI 1.138–1.175) than controls, 1.134 g/cm² (95% CI 1.127–1.141) ($p = 0.02$) (Table 1). However, there was an interaction between age and case status for hip BMD as shown in Fig. 1.

Adjusted hip BMD did not differ between 70 younger (aged 45–59) cases and 961 non-cases, 1.329 g/cm² vs. 1.335 g/cm², respectively, $p = 0.76$. In contrast, adjusted hip BMD was 0.26 standard deviation (SD) units higher in 152 cases than in 542 non-cases in the 60–79 year age group, 1.145 g/cm² (95% CI 1.122–1.163) vs. 1.106 g/cm² (1.094–1.118), $p = 0.003$ ($p = 0.055$ for age interaction).

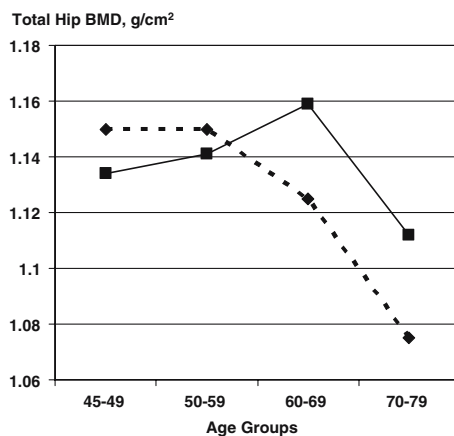
After adjustment for age and BMI in logistic regression, prostate cancer risk, in men aged 60–79, increased across quartiles of BMD (test for trend, $p = 0.004$) (Table 2). Prostate cancer risk was about two-fold higher (OR: 2.12; 95% CI: 1.21–3.71) in the highest quartile compared with the lowest quartile of hip BMD. In adjusted continuous analyses, prostate cancer risk increased 34% for each standard deviation unit of hip BMD (Table 2). Prostate cancer risk was not associated with BMD in men aged 45–59 (Table 2).

Discussion

We conducted a population-based study of the relationship between BMD, a lifetime marker of steroid hormone, growth factor, vitamin D and calcium exposure, and the risk of prostate cancer in apparently healthy men of African descent on the Caribbean island of Tobago. Screening-detected prevalence of prostate cancer was very high in this population, particularly among older men (22% of screened men aged 60–79) [3]. Total hip BMD was approximately one standard deviation higher across age groups 40–79 than

Table 1 Comparison of anthropometrics and hip bone mineral density in cases and non-cases

Variable	Cases, <i>n</i> = 222		Non-cases, <i>n</i> = 1,503		<i>p</i> -value
	Mean (number)	95% CI (percent)	Mean (number)	95% CI (percent)	
Age (year)	63.6	62.5–64.8	56.8	56.4–57.3	<0.000
Age group 45–49	(9)	(4)	(376)	(25)	
Age group 50–59	(61)	(28)	(585)	(39)	
Age group 60–69	(96)	(43)	(387)	(26)	
Age group 70–79	(56)	(25)	(155)	(10)	
Height (cm)	172.8	171.9–173.6	174.7	174.4–175.0	<0.000
Weight (kg)	81.9	80.0–83.7	82.7	82.0–83.4	0.42
BMI (kg/m ²)					
Unadjusted	27.4	26.8–27.9	27.1	26.9–27.3	0.28
Age adjusted	27.6	27.1–28.2	27.0	26.8–27.2	0.055
Total hip BMD (g/cm ²)					
Unadjusted	1.145	1.128–1.143	1.135	1.128–1.143	0.37
Age adjusted	1.164	1.144–1.184	1.133	1.125–1.140	0.004
Age, BMI adjusted	1.157	1.138–1.175	1.134	1.127–1.141	0.023

**Fig 1** Total hip BMD in Tobago prostate cancer cases and non-cases aged 45–79 years. Cases, solid line with boxes; non-cases, dashed line with diamonds

observed in African American men, and more than one standard deviation greater than observed in Caucasian American men in the National Health and Nutrition Survey (NHANES) III [27, 28]. Factors contributing to the high BMD in this population remain to be elucidated, but the high BMD is consistent with the

hypothesis of high exposure to endogenous sex steroid hormone and growth factors in the population. Among men without prostate cancer, we observed the anticipated pattern of decline in hip BMD across age groups as observed in other cross-sectional studies [27]. In contrast, BMD did not decline across age groups among the men with prostate cancer until age 70–79. The risk of prostate cancer increased with increasing BMD among older men, aged 60–79. Prostate cancer risk was two-fold higher in those in the highest quartile of BMD compared to those in the lowest quartile, independent of age and BMI.

Our results are consistent with cohort analyses among Caucasian men in the Framingham Study [25], which involved 100 cases primarily diagnosed at an older age. Incidence of prostate cancer was higher in the two upper age-specific quartiles of metacarpal cortical areas measured at mean age 61 years, with median age at prostate cancer diagnosis, 75.2 years. The relative risk for highest quartile compared with lowest was 1.6 (95% CI 0.9–3.0, *p*-value for trend across quartiles, 0.06). In contrast, the prospective NHANES I Epidemiologic Followup Study [29] found

Table 2 Odds ratio for prostate cancer by quartile of total hip BMD in Tobago men aged 45–59 years and 60–79 years

Quartile of hip BMD (g/cm ²)	Men aged 45–59				Men aged 60–79			
	Quartile range	Case (<i>n</i>)	Non-case (<i>n</i>)	OR (95% CI) (adj for BMI and age)	Quartile range	Case (<i>n</i>)	Non-case (<i>n</i>)	OR (95% CI) (adj for BMI and age)
1	0.70–1.05	12	246	1.00 (Referent)	0.61–1.01	31	143	1.00 (Referent)
2	1.06–1.14	15	242	0.99 (0.47–2.06)	1.02–1.11	32	141	1.10 (0.63–1.92)
3	1.15–1.25	26	234	1.42 (0.70–2.92)	1.12–1.20	39	135	1.46 (0.84–2.54)
4	1.25–1.63	17	239	1.01 (0.49–2.29)	1.21–1.69	50	123	2.12 (1.21–3.71)
Test for trend				<i>p</i> = 0.65				<i>p</i> = 0.004
OR per 1SD (0.15) increase in BMD				0.77 (0.73–1.28)				1.34 (1.10–1.63)

a nonsignificant trend toward lower prostate cancer incidence ($n = 94$) in the three higher BMD quartiles of radiographic estimated bone density measured at mean age 49 years in 1974–1975 and followed through 1992 for diagnosis of prostate cancer. The age, BMI and ethnicity adjusted odds ratio for highest compared with lowest quartile was 0.72 (95% CI 0.38–1.38, p -value for trend across quartiles, 0.37). Age at prostate cancer diagnosis was not reported. The potential for younger age at diagnosis of cases in the latter study, the inclusion of about 12% African Americans, and the use of BMD quartiles calculated across all age groups may have contributed to the difference between these two prospective studies.

A prospective study in older (aged 65+ years at baseline) Caucasian women [19] found a positive association between breast cancer risk and hip BMD which was of similar magnitude to the association between prostate cancer risk and hip BMD in older men observed in the current study.

The pattern of higher BMD observed in older men with prostate cancer may reflect greater peak BMD, as would result from higher steroid hormone/growth factor production early in life, or a slower decline in BMD in cases with age, as would result from maintenance of higher steroid hormone/growth factor levels into old age, or a combination of these patterns.

Endogenous levels of hormones, growth factors, or cytokines may provide a link between BMD and prostate cancer risk among older men. Androgens and estrogens are important determinants of bone density in men [30], with estrogens thought to play a relatively more important role in older men [31]. Although strong data from animal studies implicate both androgens and estrogens in the etiology of prostate cancer [32], few prospective studies or nested case–control studies have demonstrated that higher levels of serum androgens or estrogens are associated with an increased risk of prostate cancer among older men [33]. Serum levels of insulin have been associated with prostate cancer [34], and are also positively associated with BMD in men [35]. Insulin stimulates prostate cell proliferation *in vitro* [36]. Insulin-like growth factors are also important determinants of BMD [23], and serum levels have been associated with increased prostate cancer risk in several studies [14–16]. Finally, increased production of proinflammatory cytokines has been noted among individuals with low BMD [37]. *In vitro* data suggest that the proinflammatory cytokines, interleukin 1 β and tumor necrosis factor- α , may have growth-inhibitory effects on prostate cancer cells [38–40]. Thus, the relationship between BMD and prostate cancer risk may involve a complex interplay of hor-

mones, growth factors, and cytokines, and this relationship may differ by age.

An association between BMD and prostate cancer risk could be confounded by body size and adiposity. Obesity is a major determinant of BMD [41] and potential risk factor for prostate cancer [42]. In our study, men who developed prostate cancer had somewhat higher BMI than did men who did not develop prostate cancer. However, the association between BMD and prostate cancer remained after adjustment for BMI.

Our study had several strengths. It was the largest population-based study of BMD and of prostate cancer in men of African descent. Recruitment and prostate cancer screening in this prospective study were exactly the same for non-cases and prostate cancer cases reducing the likelihood of bias and misclassification. Standard, state-of-the-art BMD measurements were performed. An important limitation was our cross-sectional design. The relationship between BMD and prostate cancer is best studied in a prospective design because of the possible confounding effects of the disease on BMD, e.g., treatment, metastases, poor health. Restriction of our analyses to screening-detected cases with moderately differentiated tumors minimized the influence of ill health and metastases on BMD, but precluded study of the association of BMD to cancers which had advanced. The relatively small number of younger men with prostate cancer was a further limitation.

This is the first report to describe the relationship between BMD and the risk of prostate cancer in a population of African descent. Our results support a link between lifetime steroid hormone/growth factor exposure and the high prostate cancer risk that is characteristic of men of African descent. The lack of association of BMD with prostate cancer among the younger men suggested that other mechanisms may play a more prominent role in the etiology of early onset prostate cancer among men of African descent.

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