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# The Association of Bone Mineral Density with Prostate Cancer Risk in the Osteoporotic Fractures in Men (MrOS) Study

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## Abstract

We investigated the association of bone mineral density (BMD) measures with prostate cancer (PCa) risk in older men enrolled in the Osteoporotic Fractures in Men (MrOS) Study. We hypothesized that men with higher BMD, a marker of exposure to endogenous sex hormones, would have an increased incidence of PCa.

The cohort included 4597 men (89% white, 65 years or older) with no prior history of PCa. Baseline total body, total hip, and spine BMD were assessed using dual energy x-ray absorptiometry. Prostate cancer was confirmed by review of medical records. Cox regression was used to assess the association of BMD quartiles with incident PCa, adjusting for age, BMI, and other covariates.

During an average follow-up of 5.2 years, 5.6% (N=255) of men developed PCa. Total body BMD was inversely associated with incident PCa, with a significant trend for decreasing PCa risk with increasing BMD quartiles (p-trend=0.007). Men in the highest total body BMD quartile had a 41% reduced risk for prostate cancer (HR=0.59, 95% CI: 0.40–0.86), compared to men in the lowest quartile. Total hip and spine BMD did not exhibit significant relationships with PCa. Associations of BMD measures differed for low-grade (Gleason sum 2–6) vs. high-grade tumors (Gleason sum ≥7). Significant inverse relationships with high-grade disease were noted at the total body and total hip sites. However, no associations were observed with low-grade disease.

Our results provide support for an inverse association between BMD and prostate cancer risk. Possible pathophyisological mechanisms linking BMD and prostate cancer should be elucidated.

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***Conflict of Interest:*** None

### Keywords

Bone mineral density; prostate cancer; MrOS Study

## BACKGROUND

Prostate cancer (PCa) is the most common malignancy in men. According to the American Cancer Society, it is estimated to result in 218,890 new cases and 27,050 deaths in 2007 (1). Despite its public health burden, the etiology of PCa remains poorly understood. Apart from the established risk factors for PCa including older age, race, and family history of the disease, only a few other factors have been suggested to contribute to the development of this malignancy.

Androgens are thought to stimulate cell proliferation of the prostate epithelium and have been related to increased risk of PCa in some but not most prospective epidemiologic studies (2,3). Higher levels of insulin-like growth factor 1 (IGF-1) also have been implicated in prostate carcinogenesis (4). Additionally, high calcium intake has been associated with elevated PCa risk (5). However, evidence for the role of these factors is still inconclusive as conflicting results were reported by other studies (6,7). A common limitation of these studies was the use of a single assessment of androgens and growth factor levels. Owing to the intra-individual variations in the levels of these factors, a single measurement at one time point may not accurately reflect average or cumulative exposure.

Bone mineral density (BMD) has been regarded as a possible surrogate marker for lifetime exposure to endogenous sex hormones, IGF-1, and calcium intake (8,9). Based on this, the association of BMD with prostate cancer was examined in a few epidemiologic studies (10–12). Results from the Tobago Prostate Survey indicated a cross-sectional association between higher BMD and increased prostate cancer prevalence in Afro-Caribbean men aged 60–79 years (10). Similarly, in the Framingham Study, a trend for higher prostate cancer risk with increasing BMD quartiles was noted in Caucasian men (12). However, conflicting findings were reported in the NHANES I Epidemiologic Follow-up Survey where a non-significant decline in prostate cancer risk was observed with higher BMD (11).

The majority of these studies have not utilized state of the art assessments of bone density (11,12). While the Tobago Prostate Survey used dual-energy X-ray absorptiometry (DXA), it was cross-sectional in nature, and therefore did not account for the possible confounding effect of PCa on bone density (10). To our knowledge, no study has prospectively assessed the association of DXA-determined BMD measures with incident prostate cancer in men with no history of the disease. Additionally, it is not known whether this association varies by tumor grade.

The aim of the present study was to investigate the association of BMD measures with the subsequent development of prostate cancer in older men participating in the Osteoporotic Fractures in Men (MrOS) study. Our hypothesis was that men with higher BMD would have an increased risk of prostate cancer.

## METHODS

### Study Population

Participants were enrolled in the MrOS study, a multi-center longitudinal study evaluating risk factors and sequelae of vertebral and non-vertebral fractures in older men. The cohort included 5995 community dwelling, ambulatory men aged 65 years or older. Men were recruited from

March 2000 through April 2002 at six geographic regions of the United States: Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California. Men were not eligible for inclusion if they: (1) were unable to walk without the assistance of another person or aide, (2) had bilateral hip replacements, (3) were unable to provide self-reported data, (4) were not expected to reside near a clinical site for the duration of the study, (5) had a medical condition that (in the judgment of the investigator) would result in imminent death, or (6) were unable to understand and sign an informed consent. To qualify as an enrollee, the participant had to answer the self-administered questionnaire, attend the clinic visit, and complete at least the anthropometric, DXA, and vertebral X-ray procedures. The Institutional Review Board at each recruitment site approved the study protocol, and written informed consent was obtained from all participants (13,14).

The current analysis included 4597 participants. We excluded men with a self-reported history of prostate cancer (N= 709) or any other cancer (except for non-melanoma skin cancer) (N= 384), and men who have received osteoporosis medications (N= 90), androgen (N= 22) or antiandrogen (N= 150) therapy, or testosterone injections (N= 55).

## Prostate Cancer Diagnosis

Prostate cancer cases occurring between the baseline visit and February 2007 (range of follow-up= 0.0–6.8 years, mean= 5.2 years, median= 5.4 years) were identified through self-report using a mailed tri-annual follow-up questionnaire. For participants who did not return the questionnaire, information about events was elicited through in-person or telephone interviews. For each reported event, medical records were requested from the hospital or clinic including: pathology reports for initial diagnosis of prostate cancer, PSA lab reports prior to diagnosis, clinical notes ordering biopsy, post-diagnosis studies reports, and post-diagnosis clinic notes. Medical records were reviewed and events were adjudicated centrally at the MrOS coordinating center (University of California, San Francisco) and California Pacific Medical Center Research Institute without knowledge of BMD or other risk factors. Key prognostic characteristics of the tumor (stage and Gleason histologic scores) and type of treatment were also collected.

## BMD Measurement

Areal BMD ($g/cm^2$) measures of the total body, total hip, and spine were measured at the baseline visit using DXA (QDR 4500 W scanner, Hologic Inc., Waltham, MA, USA). Scans were performed at each study center by certified technicians using a standardized protocol for participant positioning and scan analysis. For quality assurance, the MrOS coordinating center reviewed a random subset of scans, scans with exceptionally high or low BMD, and problematic scans identified by technicians at the clinics. Cross-calibration studies were performed prior to the baseline MrOS visit. No linear differences across scanners were observed and the inter-scanner coefficient of variation was 0.9% for the hip and 0.6% for the spine.

## Covariates

At the baseline visit, participants completed a self-administered questionnaire and were interviewed and examined by trained and certified clinical staff. Demographic characteristics included age, race/ethnicity (Caucasian/White, African American/Black, Asian, Hispanic and Other) and educational level. Lifestyle risk factors included alcohol consumption (current drinking vs. not), smoking (current, past, never), and physical activity as reported on the Physical Activity Scale for the Elderly (PASE) (15). Personal history of specific medical conditions (e.g., cancer, diabetes mellitus, osteoporosis, and prostatitis) was assessed. Participants were asked to bring in current prescription medications to the clinic visit. Specific classes of medications (e.g. thiazide diuretics, oral corticosteroids, statins, osteoporosis

medications, etc) were coded by trained staff using a computerized database. The intakes of dietary calcium and vitamin D from foods and supplements were estimated using a modified Block semiquantitative food frequency questionnaire developed specifically for MrOS by Block Dietary Systems (Berkeley, CA) (16). Total intakes of calcium and vitamin D were calculated by summing dietary calcium intake (milligrams per day) and daily dosage of calcium supplements (milligrams per day). Anthropometric measures such as weight and height were measured using standard equipment, including a Harpenden stadiometer and a balanced beam or digital scale. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters.

### Data Analysis

Baseline characteristics and BMD measures of men with or without incident PCa were compared using chi-square test for categorical variables and either 2-sample t-test or Wilcoxon rank-sum test for continuous data. The incidence rate of prostate cancer was calculated as the number of cases divided by the person-years of follow-up. Follow-up time was calculated from the date of study entry to the date of prostate cancer diagnosis, death, or last contact with the participant. Cox proportional hazards regression was used to estimate the hazard ratio (HR) of incident PCa by BMD quartiles. Unadjusted and adjusted models were fitted for each BMD variable separately. Variables were selected for entry into the regression models if they were significantly associated with prostate cancer in univariate analysis. Race and body mass index were adjusted for regardless of their statistical significance. Linear trend in the risk of PCa across BMD quartiles was tested by including the median values for BMD quartiles as a single continuous variable. Additional analyses were performed to model the risk of PCa per one SD decrease in BMD (calculated as the deviation from the mean BMD divided by the standard deviation of the BMD measure). The proportional hazards assumption was checked by testing the significance of interaction terms of BMD variables with time. In secondary analyses, separate models were performed to estimate the risk of high-grade (defined as Gleason sum ≥ 7) vs. low-grade (defined as Gleason sum 2–6) tumors by BMD quartiles. The level of significance was set at 0.05. Data was analyzed using SAS version 8.01 (SAS Institute Inc, Cary, NC, USA).

## RESULTS

During an average follow-up of 5.2 years (range of follow-up= 0.0–6.8 years, median= 5.4 years), 5.5% (255 out of 4597) of the men were diagnosed with prostate cancer. The median age at diagnosis was 74.7 years. Fifty one percent of the cases had a high histologic grade (defined as Gleason sum ≥7). Based on their baseline characteristics, men with incident prostate cancer were younger, had a higher level of physical activity and daily calcium intake, and were more likely to have a family history of prostate cancer, compared to men without prostate cancer (Table 1).

For total body BMD, the incidence rates of prostate cancer (per 1000 person-years) were found to decrease by increasing BMD quartiles (12.3 in the lowest quartile, 11.7 in the second, 11.4 in the third, and 7.7 in the highest quartile). A significant trend for decreasing prostate cancer risk with increasing BMD quartiles was observed in unadjusted (p-value for trend= 0.02), age-adjusted (p-value for trend= 0.01), and multivariate models (p-value for trend= 0.007). Men in the highest total body BMD quartile had a 41% reduced risk for prostate cancer (multivariate-adjusted HR= 0.59, 95% CI: 0.40–0.86), compared to men in the lowest quartile. However, men in the second and third quartiles of BMD did not have a significant reduction in PCa risk as compared to men in the lowest quartile. When total body BMD was entered in the model as a continuous variable, each SD increase in BMD was associated with a 14% reduced risk of prostate cancer (multivariate-adjusted HR= 0.86, 95% CI: 0.75–0.98) (Table 2).

Total hip BMD was not associated with the incidence of prostate cancer in unadjusted or adjusted analyses. Compared to the lowest quartile of total hip BMD, the adjusted relative risk of prostate cancer was 0.97 (95% CI: 0.98–1.38) in the second quartile, 1.03 (95% CI: 0.72–1.46) in the third quartile, and 0.91 (95% CI: 0.62–1.33) in the highest quartile (Table 3).

Similarly, in unadjusted and adjusted Cox regression models, spine BMD was not significantly associated with the risk of prostate cancer (Table 4).

Associations of BMD measures differed for low-grade vs. high-grade tumors. A significant inverse relationship was observed for total body BMD with high-grade PCa. A significant trend for lower high-grade PCa risk was observed with increasing BMD quartiles (p for trend= 0.01), with men in the highest quartile having a 57% reduced risk, compared to men in the lowest quartile (HR= 0.43, 95% CI 0.25–0.74). For total hip BMD, men in the second quartile had a 46% reduced risk of high-grade disease, as compared to men in the first quartile (HR= 0.54, 95% CI 0.32–0.92). On the other hand, none of the BMD measures was significantly associated with the risk of developing low-grade PCa (Table 5).

## DISCUSSION

This prospective analysis evaluated the association of BMD measures with incident prostate cancer in a cohort of older men with no history of PCa. Unexpectedly, we found that higher BMD of the total body was significantly related to reduced risk for prostate cancer. No associations were observed for hip and spine BMD measures with PCa. Additionally, total body BMD was inversely associated with the development of high-grade, but not low-grade disease. A similar but weaker association was observed for total hip BMD with high-grade PCa.

The direction of the association of total body BMD with prostate cancer was contrary to our initial hypothesis. This finding lends support to results from the NHANES I Epidemiologic Follow-up Survey where a decline in prostate cancer risk, although not significant, was observed with higher quartiles of bone density, determined using radiographic absorptiometry. In that study, compared to the lowest BMD quartile, the age, race, and BMI-adjusted rate ratios across BMD quartiles were 0.63 (95% CI: 0.37–1.07) for the second, 0.86 (95% CI: 0.49–1.49) for the third, and 0.72 (95% CI: 0.38–1.38) for the highest quartile (11).

Our results were discordant with those from the Tobago Prostate Survey and the Framingham Study, where higher bone density was associated with an increased prostate cancer risk (10, 12). The Tobago study evaluated Afro-Caribbean men, and reported a significant trend of higher prostate cancer prevalence with increasing total hip BMD quartiles, in men aged 60–79 years. Compared to men in the lowest quartile of BMD, those in the highest quartile had a two-fold higher odds of prostate cancer (OR= 2.12, 95% CI: 1.21–3.71). No such associations were observed in younger men in this cohort (10). Notably, total hip BMD in this population was higher than that observed for African-American men in NHANES III by approximately one standard deviation (17). This may be reflective of a higher exposure to endogenous sex steroid hormones and growth factors. The Framingham study involved 100 cases of prostate cancer, diagnosed at a median age of 75.2 years. It reported a higher risk of PCa in the upper two quartiles of radiogrammetrically-determined metacarpal cortical width, assessed at a mean age of 61 years (12). While these findings were adjusted for important risk factors such as age and BMI, they may be prone to residual confounding by factors such as family history of prostate cancer and calcium and vitamin D intakes, which were not collected in the above studies.

Sex steroids are important regulators of skeletal growth and maintenance of BMD in both men and women (18,19). In the Swedish arm of the MrOS cohort, free testosterone was found to

be a positive predictor of bone density at the total body, total hip, femur trochanter, and arm (20). Androgens are also thought to stimulate cell proliferation of the prostate epithelium and were related to increased risk of PCa in some prospective epidemiologic studies (2,3). While the direction of association observed in our study does not provide a direct evidence for the role of endogenous sex hormones in the link between BMD and prostate cancer, it suggests a possible involvement of other pathophysiological mechanisms.

Poor vitamin D status may be a common denominator for the inverse association between BMD and prostate cancer risk. Low levels of vitamin D are known to have detrimental effects on bone density (21) and have been implicated in prostate carcinogenesis. In-vivo evidence suggests that calcitriol has anti- proliferative and chemopreventive effects in PCa (22). Additionally, in some epidemiologic studies, low levels of vitamin D metabolites have been assocaited with increased prostate cancer risk (23,24).

Inflammation may also be involved in the link between BMD and prostate cancer. Pro-inflammatory cytokines have been implicated in osteoporosis and increased fractures risk (25,26). Interleukin-6 was shown to stimulate osteoclasts, thereby increasing the rates of bone remodeling and bone loss (26). Inflammation is also suggested to play a role in prostate carcinogenesis (27). In the MrOS cohort, self-reported history of prostatitis was found to be positively associated with prevalent prostate cancer (OR= 5.4, 95% CI 4.4–6.6) (28), raising the possibility that chronic inflammation within the prostate may contribute to the pathogenesis of prostate cancer. Owing to the complex multifactorial pathogenesis of prostate cancer and bone mineralization, it is likely that more than one biological mechanism is involved in their link.

Interestingly, in our secondary analysis, the relationship of BMD measures with prostate cancer was limited to high-grade tumors. To our knowledge, our study was the first to investigate the relationship of bone density with tumor grade in PCa. Therefore, no other data are available for direct comparison. Vitamin D insufficiency may be involved in this association. Recent results from the Physician's Health Study have indicated that low levels of both 25(OH) D and $1,25(OH)_2D$ were related to increased risk of aggressive PCa. However, no such associations were observed for non-aggressive disease (24).

The observed associations were specific to BMD of the total body as well as the total hip, in the case of high grade disease. The lack of association at the spine may be related to the sensitivity of DXA technology to extra-osseous calcification, such as aortic calcification and degenarative osteoarthritic changes, which get incorporated in the region of interest and lead to a falsely increased bone density of the spine.

Interestingly, we observed that men with incident PCa were younger and had a higher level of physical activity, compared to men who did not develop the disease. This may be a reflection of increased awareness to prostate cancer screening and prevention in PCa cases, as triggered by their stronger family history of the disease.

Our results extend previous findings by longitudinally examining the association of prostate cancer and tumor grade with bone density at different skeletal sites. Our study had the benefit of a rigorous adjudication of prostate cancer cases, determination of BMD using a state-of-the-art method, and adjustment of results for a comprehensive set of risk factors for PCa, including calcium intake, family history of PCa, physical activity, and statin use. Limitations of our analysis include the unavailability of serum measurements of vitamin D and sex hormones on the full population, and the generalizability of findings to other populations due to the inclusion of a well-functioning cohort of mainly older white men.

In conclusion, we observed an unexpected inverse association between total body bone density and the risk of prostate cancer in older men who did not have a prior history of the disease. Further research is needed to confirm the direction of the relationship and to elucidate the pathophysiological mechanisms involved in the link between BMD and prostate cancer.

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**Table 1**

Baseline characteristics and bone mineral density measures (mean ± SD, N (%)) by prostate cancer status in the MrOS cohort

| | Incident prostate cancer (N= 255) | No prostate cancer (N= 4342) | P-value |
|---|---|---|---|
| Age at baseline | 72.4 ± 5.1 | 73.2 ± 5.8 | 0.02 |
| Age at diagnosis of prostate cancer | 75.4 ± 5.3 | - | |
| Race | | | 0.88 |
| White | 229 (89.8) | 3864 (89.0) | |
| African American | 12 (4.7) | 176 (4.0) | |
| Asian | 7 (2.8) | 147 (3.4) | |
| Hispanic | 4 (1.6) | 102 (2.3) | |
| Other | 3 (1.2) | 53 (1.2) | |
| Educational level | | | |
| College or higher | 130 (51.0) | 2285 (52.6) | 0.61 |
| Smoking status | | | 0.20 |
| Current smoker | 7 (2.6) | 169 (3.9) | |
| Past smoker | 141 (55.3) | 2574 (59.3) | |
| Alcohol consumption | 173 (68.4) | 2799 (64.5) | 0.21 |
| (% who had12 drinks in past month) | | | |
| Physical activity (PASE score) | 159.8 ± 72.7 | 148. ± 68.1 | 0.007 |
| Weight (kg) | 82.2 ± 12.3 | 83.3 ± 13.4 | 0.20 |
| Height (cm) | 174.1 ± 6.8 | 174.2 ± 6.8 | 0.77 |
| BMI ($Kg/m^2$) | 27.1 ± 3.5 | 27.4 ± 3.8 | 0.21 |
| Weight change since age 25 (Kg) | 10.2 ± 10.8 | 10.3 ± 11.4 | 0.88 |
| Calcium intake from diet and supplements (mg/day) | 1197.3 ± 575.3 | 1108.6 ± 581.8 | 0.02 |
| Vitamin D intake from diet and supplements (IU/day) | 409.7 ± 240.5 | 384.3 ± 244.1 | 0.11 |
| Family History of prostate cancer | 48 (18.8) | 557 (12.8) | 0.006 |
| Medical History | | | |
| History of osteoporosis | 6 (2.4) | 73 (1.7) | 0.45 * |
| History of diabetes | 22 (8.6) | 479 (11.0) | 0.23 |
| History of prostatitis | 61 (23.9) | 862 (19.8) | 0.11 |
| Medications | | | |
| Thiazide diuretics | 32 (12.6) | 470 (10.8) | 0.39 |
| Oral corticosteroids | 1 (0.4) | 69 (1.6) | 0.18 * |
| Statins | 78 (30.6) | 1101 (25.4) | 0.06 |
| Histologic Grade | | | |
| Low (Gleason sum 2–6) | 122 (47.8) | - | |
| High (Gleason sum ≥7) | 129 (50.6) | | |
| Unknown | 4 (1.6) | | |
| Total Body BMD ($g/cm^2$) † | 1.16 ± 0.12 | 1.18 ± 0.12 | 0.05 |
| Total hip BMD ($g/cm^2$) ‡ | 0.96 ± 0.14 | 0.96 ± 0.14 | 0.81 |
| Spine BMD ($g/cm^2$) § | 1.06 ± 0.17 | 1.08 ± 0.18 | 0.29 |

| | Incident prostate cancer (N= 255) | No prostate cancer (N= 4342) | P-value |
|---|---|---|---|

*P-value for Fisher's Exact test

†Total body BMD is missing for 28 participants.

‡Hip BMD is missing for 1 participant.

§Spine BMD is missing for 5 participants.

**Table 2**

Risk of prostate cancer by baseline total body BMD quartiles in the MrOS cohort

| Total body BMD ($g/cm^2$) | Quartile Range ($g/cm^2$) | Number at risk (events) | Incidence rate (cases per 1000 person-years) | Unadjusted hazard ratio (95% CI) | Age-adjusted hazard ratio (95% CI) | Multivariate hazard ratio (95% CI) * |
|---|---|---|---|---|---|---|
| First Quartile | 0.80–1.09 | 1142 (72) | 12.3 | 1.00 | 1.00 | 1.00 |
| Second Quartile | 1.09–1.17 | 1142 (69) | 11.7 | 0.95 (0.68–1.32) | 0.94 (0.67–1.3) | 0.91 (0.66–1.27) |
| Third Quartile | 1.17–1.25 | 1143 (67) | 11.4 | 0.92 (0.66–1.29) | 0.90 (0.64–1.26) | 0.90 (0.64–1.26) |
| Fourth Quartile | 1.25–2.04 | 1142 (46) | 7.7 | 0.63 § (0.44–0.91) | 0.61 ‖ (0.42–0.89) | 0.59 ‖ (0.40–0.86) |
| *P-value for trend* | | | | 0.02 | 0.01 | 0.007 |
| HR per 1 SD † | | | | 0.88 § | 0.87 § | 0.86 § |
| increase in BMD | | | | (0.77–1.00) | (0.76–0.99) | (0.75–0.98) |

* Adjusted for age, race, BMI, family history of prostate cancer, physical activity, statin use, and calcium intake

† Total body BMD: SD= 0.12 $g/cm^2$

§ P-value <0.05

‖ P-value <0.01

**Table 3**

Risk of prostate cancer by baseline total hip BMD quartiles in the MrOS cohort

| Total hip BMD ($g/cm^2$) | Quartile Range ($g/cm^2$) | Number at risk (events) | Incidence rate (cases per 1000 person-years) | Unadjusted hazard ratio (95% CI) | Age-adjusted hazard ratio (95% CI) | Multivariate hazard ratio (95% CI) * |
|---|---|---|---|---|---|---|
| First Quartile | 0.31–0.87 | 1149 (64) | 10.9 | 1.00 | 1.00 | 1.00 |
| Second Quartile | 0.87–0.96 | 1149 (63) | 10.7 | 0.97 (0.69–1.38) | 0.95 (0.67–1.35) | 0.97 (0.68–1.38) |
| Third Quartile | 0.96–1.05 | 1149 (67) | 11.2 | 1.03 (0.73–1.45) | 1.00 (0.71–1.41) | 1.03 (0.72–1.46) |
| Fourth Quartile | 1.05–1.76 | 1149 (61) | 10.2 | 0.93 (0.66–1.32) | 0.89 (0.63–1.27) | 0.91 (0.62–1.33) |
| *P-value for trend* | | | | 0.76 | 0.59 | 0.69 |
| HR per 1 SD † | | | | 0.97 | 0.96 | 0.96 |
| increase in BMD | | | | (0.86–1.10) | (0.84–1.09) | (0.84–1.10) |

*Adjusted for age, race, BMI, family history of prostate cancer, physical activity, statin use, and calcium intake

†Total hip BMD: SD= 0.14 $g/cm^2$

**Table 4**

Risk of prostate cancer by baseline spine BMD quartiles in the MrOS cohort

| Spine BMD ($g/cm^2$) | Quartile Range ($g/cm^2$) | Number at risk (events) | Incidence rate (cases per 1000 person-years) | Unadjusted hazard ratio (95% CI) | Age-adjusted hazard ratio (95% CI) | Multivariate hazard ratio (95% CI) * |
|---|---|---|---|---|---|---|
| First Quartile | 0.47–0.94 | 1148 (56) | 9.4 | 1.00 | 1.00 | 1.00 |
| Second Quartile | 0.94–1.06 | 1148 (73) | 12.4 | 1.31 (0.93–1.86) | 1.31 (0.92–1.85) | 1.31 (0.92–1.86) |
| Third Quartile | 1.06–1.18 | 1148 (70) | 11.9 | 1.26 (0.89–1.79) | 1.26 (0.89–1.80) | 1.29 (0.90–1.84) |
| Fourth Quartile | 1.18–2.10 | 1148 (54) | 9.1 | 0.97 (0.67–1.41) | 0.98 (0.68–1.43) | 0.98 (0.67–1.44) |
| *P-value for trend* | | | | 0.84 | 0.93 | 0.94 |
| HR per 1 SD † | | | | 0.94 | 0.94 | 0.94 |
| increase in BMD | | | | (0.83–1.06) | (0.83–1.07) | (0.83–1.08) |

*Adjusted for age, race, BMI, family history of prostate cancer, physical activity, statin use, and calcium intake

†Spine BMD: SD= 0.24 $g/cm^2$

**Table 5**

Risk of high grade and low grade prostate cancer by baseline total body, total hip, and spine BMD quartiles in the MrOS cohort

| | **High Grade PCa (Gleason sum ≥7)** | | **Low Grade PCa (Gleason sum 2–6)** | |
|---|---|---|---|---|
| | Number at risk (events) | Multivariate hazard ratio (95% CI) * | Number at risk (events) | Multivariate hazard ratio (95% CI) * |
| Total body BMD (g/cm$^2$) | | | | |
| First Quartile | 1111 (41) | 1.00 | 1100 (30) | 1.00 |
| Second Quartile | 1100 (27) | 0.64 (0.40–1.04) | 1113 (40) | 1.23 (0.76–1.98) |
| Third Quartile | 1115 (39) | 0.93 (0.60–1.44) | 1103 (27) | 0.85 (0.50–1.43) |
| Fourth Quartile | 1117 (21) | 0.43 (0.25–0.74) † | 1121 (25) | 0.79 (0.46–1.36) |
| *P-value for trend* | | 0.01 | | 0.21 |
| Total hip BMD (g/cm$^2$) | | | | |
| First Quartile | 1125 (40) | 1.00 | 1108 (23) | 1.00 |
| Second Quartile | 1108 (22) | 0.54 (0.32–0.92) ‡ | 1125 (39) | 1.67 (0.99–2.82) |
| Third Quartile | 1119 (37) | 0.86 (0.54–1.38) | 1111 (29) | 1.28 (0.73–2.24) |
| Fourth Quartile | 1118 (30) | 0.63 (0.38–1.06) | 1119 (31) | 1.41 (0.80–2.50) |
| *P-value for trend* | | 0.21 | | 0.46 |
| Spine BMD (g/cm$^2$) | | | | |
| First Quartile | 1121 (29) | 1.00 | 1118 (26) | 1.00 |
| Second Quartile | 1115 (40) | 1.40 (0.87–2.26) | 1108 (33) | 1.26 (0.75–2.13) |
| Third Quartile | 1108 (30) | 1.03 (0.62–1.72) | 1116 (38) | 1.59 (0.96–2.62) |
| Fourth Quartile | 1123 (29) | 0.91 (0.54–1.54) | 1118 (24) | 1.07 (0.61–1.87) |
| *P-value for trend* | | 0.43 | | 0.51 |

* Adjusted for age, race, BMI, family history of prostate cancer, physical activity, statin use, and calcium intake

† $p < 0.01$

‡ $p < 0.05$