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Higher Bone Mineral Density is Associated with a Decreased Risk of Colorectal Adenomas

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Abstract

Bone mineral density (BMD) is a biomarker for cumulative exposure to multiple factors including estrogen, calcium, vitamin D and physical activity, which have all been independently associated with colorectal cancer. Furthermore, higher levels of BMD have been inversely associated with colorectal cancer risk, particularly in postmenopausal women. However, no prior studies have examined the potential association between BMD and colorectal adenomas, which are precursor lesions to most colorectal cancers. Therefore, we evaluated the association between BMD, which was measured using a whole body, dual-energy X-ray absorptiometry scan, and colorectal adenomas in 167 patients who underwent colonoscopy screening. We found that patients in the highest tertile of total body BMD (>1.294 g/cm^2) and in the middle tertile (≥1.167 to ≤1.294 g/cm^2) compared to those with a total body BMD in the lowest tertile (<1.167 g/cm^2) had a lower risk of colorectal adenomas (highest vs. lowest tertile: OR=0.29 (0.10–0.84); middle vs. lowest tertile: OR=0.26 (0.08–0.80); p-trend=0.02). Stratification by gender revealed that this association was more pronounced in women (highest (>1.280 g/cm2) vs. lowest (<1.130 g/cm2) tertile: OR=0.08 (0.01–0.70); middle (≥1.130 to ≤1.280 g/cm2) vs. lowest tertile: OR=0.15 (0.04–0.94); p-trend=0.02) even after excluding hormone replacement therapy users (highest (>1.295 g/cm2) and middle (≥1.132 to ≤1.295 g/cm2) vs. lowest (<1.132 g/cm2) tertile: OR=0.17 (0.03–0.97); p-trend=0.04). Our results show, for the first time, that BMD is inversely associated with colorectal adenomas, particularly in women. Although additional larger, prospective studies are needed, our results suggest that BMD may be a biomarker for colorectal cancer precursor lesions.

Keywords

Bone mineral density; colorectal adenomas; biomarkers

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Introduction

Colorectal cancer is the third most common non-skin cancer and the third leading cause of cancer death among men and women in the U.S. (1). The majority of colorectal cancers are believed to originate through the adenoma-(progression)-to-carcinoma paradigm (2); and, removing adenomas through colonoscopy has been estimated to decrease future colorectal cancer by 76% to 90% (3). Nevertheless, the persistence of colorectal cancer, which continues to affect over 150,000 individuals and account for over 50,000 deaths annually in the U.S. despite increased colonoscopy screening and subsequent adenomatous polyp removal (4, 5), suggests there is a need for identifying additional early detection markers.

Colorectal adenomas may arise through genetic syndromes such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC); however, the majority of sporadic adenomas appear to have a strong environmental component with increasing age, smoking and alcohol being associated with increased risk and, physical activity and non-steroidal anti-inflammatory drug (NSAID) being associated with a decreased risk (6–8).

Higher dietary intakes of calcium and circulating levels of vitamin D metabolites have been inversely associated with the risk of colorectal cancer (9–11) and colorectal adenomas (12–14). Calcium and vitamin D may act synergistically to decrease adenoma recurrence as evidenced, most notably, by the reduction in recurrence only among those patients who received calcium supplements and had higher serum levels of 25-hydroxy-vitamin D (25(OH)D) in the Calcium Polyp Prevention Study (15). Higher calcium levels have been shown to exert an anti-neoplastic effect in the colon epithelium by inducing higher levels of apoptosis (16, 17). Vitamin D also helps to maintain calcium homeostasis and may act directly on the colon epithelium by regulating apoptosis and cellular differentiation and by modulating growth factor and cytokine levels (18).

Exogenous hormone use among older and primarily postmenopausal women with lower endogenous production of estrogen has been shown to decrease the risk of colorectal cancer (19, 20, 20) as well as distal (21) and larger (≥ 1 cm) (22) colon adenomas. Although the exact mechanism driving this putative preventive effect is not known, estrogen's ability to reverse age related decreases in calcium absorption and to increase serum levels of $25(OH)D_3$ and $1\alpha\text{-}25(OH)_2D_3$, the active form of vitamin D, which also affects bone metabolism, may play a role (23).

Bone mass as measured by bone mineral density (BMD) has been proposed as a marker of the cumulative exposure to endogenous and exogenous estrogens (24–26). However, BMD also reflects an individual's lifetime exposure to calcium and the intake of other vitamins and minerals that affect calcium absorption and deposition, such as vitamin D, as well as exercise, particularly weight bearing exercise (27, 28). In addition, there is some evidence that smoking and alcohol use may affect BMD levels (29, 30). Thus, BMD may serve as a composite marker for an individual's long term, synergistic exposure to several factors which, interestingly, have all been shown to be independently associated with the risk of colorectal cancer and adenomas including calcium, vitamin D, estrogen, smoking, and alcohol, as discussed above, as well as physical activity (31–34). Furthermore, utilizing BMD as an objective marker for long-term exposure to all of these factors combined may be particularly appealing due to the measurement error, bias and other problems associated with assessing lifetime lifestyle patterns using self-reported questionnaires and snap-shot serum biomarker data (35–37).

Higher BMD levels have been inversely associated with colorectal cancer (38) and colon cancer in postmenopausal women (39, 40). However, no prior studies have examined the

potential association between BMD and colorectal adenomas. Therefore, we evaluated the potential association between BMD using a whole body dual-energy X-ray absorptiometry (DXA) scan and colon adenomas in 167 patients who underwent colonoscopy screening at University Hospitals in Cleveland, Ohio. We hypothesized that higher bone mineral density would be inversely associated with colorectal adenoma risk.

Materials and Methods

Study Population

The study population consisted of a subset of patients from a larger study conducted in the greater Cleveland, Ohio region involving patients undergoing routine colonoscopy screening at the University Hospitals Health System (UHHS) from January, 2006 through August, 2009. Patients were required to complete an initial screening questionnaire over the telephone to determine if they were eligible to participate in the study. Patients who reported having a personal history of any cancer, ulcerative colitis or Crohn's disease, prior colorectal adenomatous polyps, a family history of HNPCC or FAP, or that were younger than 30 years old were excluded from further consideration.

Eligible patients having histologically confirmed adenomatous polyps in their colon and rectum, including tubular, sessile serrated or tubulovillous subtypes, were defined as cases. Patients with histologically confirmed colorectal cancer found during the colonoscopy were excluded. In the larger study, less than 1% of the patients were excluded for a diagnosis of colorectal cancer and no patients in this sub-study were excluded for a diagnosis of colorectal cancer. Patients who had hyperplastic polyps or no observed adenomas (negative colonoscopy) were included as controls in this study.

The recruitment rate among eligible participants was approximately 64.9 percent for this study. Subjects who declined to participate were demographically similar to those who agreed to participate. Specifically, patients who declined to participate compared to those who enrolled were of similar age (55.2 vs. 56.3 years), gender (59.6% vs. 52.7% female) and ethnic composition (60.4 vs. 67.1% Caucasian; 37.1 vs. 32.9% African-American). The study protocol was approved by the Institutional Review Boards of University Hospitals Case Medical Center and the Cleveland Clinic.

BMD and Other Risk Factor Measures

Eligible patients were required to complete a computer-aided personal interview (CAPI), prior to their colonoscopy, to assess lifestyle and behavioral risk factors. The CAPI was based on a risk factor questionnaire developed by the National Cancer Institute Colon Cancer Familial Cancer Registry (http://epi.grantss.cacner.gov/documents/CFR/center_questionnaires/Colon/LA/ColonRiskFactor_USC.pdf). A positive family history of colorectal cancer was defined as having one or more first degree relatives with colon or rectal cancer. Smokers were defined as patients who reported ever smoking cigarettes for 6 months or longer. Alcohol users were defined as those subjects who reported regular intake of alcohol defined as two or more drinks/week for six months or longer. Non-steroidal anti-inflammatory drug users were defined as subjects who reported using aspirin or ibuprofen at least twice a week for one month or longer.

Patients were also required to complete a validated semi-quantitative food frequency questionnaire (FFQ) (41) and a validated physical activity questionnaire (PAQ) (42) prior to their colonoscopy. Total daily intake values for calcium and vitamin D were determined by combining the values from the FFQ (41) for daily food and supplement intake reported in the year prior to colonoscopy. Physical activity was quantified from the PAQ (42) using the

total frequency, duration and intensity reported for leisure time and recreational activities in the year prior to colonoscopy.

Subjects enrolled in the sub-study were also required to complete body composition testing, which included measurement of their height and weight (without shoes and in a gown) and completion of a whole body dual-energy X-ray absorptiometry (DXA) scan (Lunar iDXA™, GE Healthcare, Madison, WI) that was conducted at the Cleveland Clinic. Body mass index (BMI) was calculated as the ratio of measured weight in kilograms divided by height in meters squared. Total body and regional site (pelvis, spine) BMD were obtained by dividing the bone mineral content (BMC) by the projected area scanned using the Lunar iDXA™ software (GE Healthcare, Madison, WI).

Menopause was confirmed by the absence of menses for at least 12 months (as self-reported in the CAPI) and by high serum levels of follicle-stimulating hormone (FSH >40 mIU/mL) and/or low serum levels of estradiol (E2 <20 pg/mL). A 43 year old female who reported an absence of menses for at least 12 months and no HRT use was observed to have a FSH level of 4.18 mIU/mL and E2 level of 144 pg/mL; and, since we could not fully resolve her post-menopausal status, she was excluded from all analyses involving the menopause variable. Venous blood samples were collected just prior to colonoscopy and placed in polystyrene tubes containing sodium EDTA (1 mg/mL). The EDTA-containing tubes were chilled promptly in an ice bath and serum was separated by centrifugation at 1000g at room temperature for 15 minutes. Serum samples were stored at −80°C until assays were conducted. The FSH and E2 assays were run using commercial Coat-a-Count immunoradiometric assay (IRMA) and radioimmunoassay (RIA) kits, respectively (Siemans Medical Solutions Diagnostics, Los Angeles, CA). All samples were run in duplicate. The intra-assay coefficient of variation was 3.8% and 6.9% for FSH and E2, respectively. The inter-assay coefficient of variation was 3.9% and 5.5% for FSH and E2, respectively.

Statistical Analysis

We used unconditional logistic regression modeling to evaluate the potential associations between BMD and colorectal adenoma risk. We defined BMD tertiles using cut-point values observed in control subjects for each region (total body, pelvis, spine), separately; and, for male and female controls in each region separately for analyses stratified by gender. We employed a modeling strategy that evaluated minimally adjusted and a more fully adjusted model since the risk factors included in prior studies reporting an association between BMD and colorectal cancer varied. Following Nelson et al. (38), we evaluated a “minimally adjusted” model that included BMD, age, gender, race and BMI. In addition, we evaluated a “full” model (Model 1) similar to that of Zhang et al. (40) that included age, gender, race and BMI as well as other known factors for colorectal adenoma risk including family history of colon cancer, NSAID use, smoking, alcohol, physical activity, total calcium intake, total vitamin D intake and total energy intake.

We stratified our analyses by gender and menopausal status. Due to the small number of premenopausal women in our study population, we were unable to investigate this subgroup. Stratified analyses conducted in females were additionally adjusted for pre- vs. post-menopausal status, age at menopause and years of hormone replacement therapy (HRT) use. Because we were unable to fully characterize the type of HRT use, we also performed the analyses with HRT users excluded (Model 2).

All p-values reported are from two-sided tests. All analyses were undertaken with SAS (Version 9.1.3, SAS Institute Inc., Cary, NC).

Results

The characteristics of the colorectal adenoma screening study population are summarized in Table 1. In general, cases were similar to controls. However, cases were more likely to be male (61.2% vs. 38.8%; p<0.01) and older (58.6 ± 7.9 (yrs.) vs. 54.8 ± 7.4 (yrs); p<0.01) compared to controls. Cases also had a marginally significantly lower mean total daily calcium intake (1129.72 ± 615.38 (g/day) vs. 1313.39 ± 650.51 (g/day); p=0.07) and female cases had an earlier age at menopause (42.5 ± 8.9 vs. 46.5 ± 7.0 (yrs); p=0.08) compared to controls.

We found an inverse association between higher total body BMD and colorectal adenomas in a minimally adjusted model that included BMD, age, gender, race and BMI (not shown). Specifically, subjects in the highest tertile (≥1.294 g/cm^2) compared to those in the lowest tertile (<1.167 g/cm^2 (lowest tertile) had a significantly lower risk of colon adenomas (OR=0.34; 95% C.I.: 0.13–0.93; p=0.03) (not shown). A marginal inverse association was observed in subjects in the middle tertile (≥1.167 to <1.294 g/cm^2) compared to the lowest tertile (OR=0.42; 95% C.I.: 0.17–1.05; p=0.07) and the p-value for trend was 0.03. Adjustment for additional risk factors (Model 1, Table 2) improved precision and decreased effect estimates slightly but did not meaningfully change results (highest tertile vs. lowest tertile: OR=0.26; 95% C.I.: 0.08–0.80; p=0.02; middle vs. lowest tertile: OR=0.29; 95% C.I.: 0.10–0.84; p=0.02; p-trend=0.02). When evaluating BMD tertiles in the pelvic region, we found that subjects with a BMD exceeding 1.162 g/cm^2 (highest tertile) compared to those with a BMD less than 1.001 g/cm^2 (lowest tertile) had a decreased risk (OR=0.39; 95% C.I.: 0.15–1.00; p=0.05; p-trend=0.05). When examining the spinal region, subjects in the highest BMD tertile (≥1.220 g/cm^2) compared to those in the lowest tertile (<1.050 g/cm^2) had a marginally reduced risk of colorectal adenomas (OR=0.42; 95% C.I.: 0.16–1.13; p=0.09). Results for more fully adjusted models (Model 1, Table 2) in pelvic and spinal regions were similar to their respective minimally adjusted models.

Because we were not able to fully characterize the type of hormone replacement therapy (HRT) use in females, we also performed the analyses with HRT users excluded. As shown in Model 2 (Table 2), we found a significant inverse association between total body BMD and colorectal adenomas when comparing the highest (>1.301 g/cm^2) and middle (≥1.169–≤1.301 g/cm^2) with the lowest (<1.169 g/cm^2) tertile (OR=0.38; 95% C.I.: 0.14–0.99; p=0.05). We observed a marginally statistically significant association between spinal region BMD and adenomas when comparing the highest (>1.223 g/cm^2) and middle (≥1.068–≤1.223 g/cm^2) versus the lowest (<1.068 g/cm^2) tertile when excluding HRT users (OR=0.39; 95% C.I.: 0.14–1.02; p=0.05).

Stratification by gender revealed that these associations were generally more pronounced among females (Table 3) compared to males (Table 4). Specifically, women with a total body BMD in the highest and middle tertiles combined compared to those in the lowest tertile had a lower colorectal adenoma risk (OR=0.29; 95% C.I.: 0.08–0.99; p=0.05) in the minimally adjusted model. Adjustment for additional risk factors (Model 1, Table 3) improved precision slightly when comparing women with total body BMD in the highest tertile (OR=0.08; 95% C.I.: 0.01–0.70; p=0.02) and middle tertile (OR=0.15; 95% C.I.: 0.04–0.94; p=0.04) to the lowest tertile (p-trend=0.02). When excluding HRT users (Model 2, Table 3), we observed similar results for total body BMD when comparing the highest (OR=0.06; 95% C.I.: 0.01–0.75; p=0.03) and middle (OR=0.16; 95% C.I.: 0.02–1.03; p=0.07) to the lowest tertile (p-trend=0.04).

In the spinal region, women in the highest (OR=0.24; 95% C.I.: 0.06–0.94; p=0.04) and middle (OR=0.16; 95% C.I.: 0.03–0.84; p=0.03) BMD tertiles compared to those in the

lowest tertile had a lower risk (p-trend=0.02) in the minimally adjusted model (not shown). Results for the more fully adjusted model (Model 1, Table 3) and the model excluding HRT users (Model 2, Table 3) were similar. In the pelvic region, women in the highest and second-highest BMD tertiles combined compared to those in the lowest tertile had a decreased risk of adenomas in minimally adjusted (OR=0.27; 95% C.I.: 0.08–0.94; p=0.04) and more fully adjusted (OR=0.14; 95% C.I.: 0.03–0.73; p=0.02) models; however, the association was only marginally significant when excluding HRT users (OR=0.21; 95% C.I.: 0.03–1.08; p=0.09).

In males, a significant association was observed in the fully adjusted model (Model 1, Table 4) when comparing men in the middle tertile to men in the lowest tertile of total body BMD (OR=0.23; 95% C.I.: 0.05–0.98; p=0.05); however, the p-value for trend was only 0.10. Although the risk of colorectal adenomas tended to decrease with increasing BMD in pelvic and spinal regions in males, we did not observe any statistically significant associations in minimally or fully adjusted models (Model 1, Table 4).

In addition, we found that postmenopausal women in the highest and middle tertiles combined compared to those in the lowest tertile of total body BMD had a lower risk of colorectal adenomas when including (OR=0.08; 95% C.I.: 0.01–0.83; p=0.02) and excluding (OR=0.04; 95% C.I.: 0.01–0.52; p=0.02) HRT users (not shown). An inverse association was also observed for spinal BMD when comparing the highest and middle tertiles combined compared to the lowest tertile when including (OR=0.08; 95% C.I.: 0.01–0.75; p=0.03) and excluding (OR=0.05; 95% C.I.: 0.01–0.75; p=0.04) HRT users. In the pelvic region, a significant inverse association was observed when including (OR=0.06; 95% C.I.: 0.01–0.62; p=0.01) but not when excluding (OR=0.09; 95% C.I.: 0.01–0.62; p=1.11) HRT users. Due to the small number of premenopausal women in our study, we could not examine potential associations between BMD and adenomas in premenopausal women.

Discussion

Our results show, for the first time, that total body BMD is inversely associated with colorectal adenomas. Stratification by gender revealed that the associations were generally more pronounced among females in our study population even when HRT users were excluded. Postmenopausal women in the highest and middle tertiles of total body BMD combined compared to those in the lowest tertile were also observed to have a decreased risk of adenomas. Associations between pelvic and spinal region BMD were similar to those observed for total body BMD.

Although our results are not directly comparable to previous findings in colorectal cancer, under the adenoma-to-carcinoma paradigm (2), our findings are indeed consistent with and complement prior studies reporting that higher bone mass levels decrease the risk of colorectal cancer (38) and colon cancer in postmenopausal women (39, 40). Differences in the specific bone mass regions examined and certain population attributes may also help explain variation in effect sizes across studies. For example, we found that the highest and middle tertiles of *spinal* (>1.209 g/cm^2; 1.017–1.209 g/cm^2) and *total body* (>1.280 g/cm^2; 1.130–1.280 g/cm^2) BMD in *females*, who were *~57* years old on average, reduced risk of colon adenomas by approximately *80% to 85%*, respectively; and, this risk was further reduced (*~90%*) in *postmenopausal* women. Ganry et al. (39) observed that the highest compared to the lowest BMD tertile in the *femoral neck* (>0.819 vs. <0.708 g/cm^2), *trochanteric* (>0.734 vs. <0.622 g/cm^2) and *Ward's triangle* (>0.655 vs. <0.546 g/cm^2) regions, which are sites previously used to diagnose osteoporosis (43), decreased the risk of *colon cancer* by about *20%* in older (mean age of *~71* years), *postmenopausal* women. When comparing the highest to the lowest BMD tertiles in the *metacarpal cortical* area

(tertile values not reported), Zhang et al. (40) found a *60%* decreased risk of colon cancer among older (mean age of *~62* years), *postmenopausal* women. Using data from the first National Health and Nutrition Examination Survey (NHANES I), which consisted of 2,818 *men* and 3,228 *women* who were, on average, *~50* years old, Nelson et al. (38) observed a significant trend for a decreasing risk of colorectal cancer with increasingly higher BMD quartiles in the left *hand* using Radiography Absorptiometry (RA). Although measures of bone density using RA have been shown to correlate with those from DXA scans, RA has several limitations including its calibration in arbitrary units (44), which inhibits the ability to direct compare bone density levels. Furthermore, the composition of bone varies by anatomical region, with the spine and pelvis having a higher concentration of metabolically active trabecular bone and the femur and legs having more cortical bone (45). Menopause also results in significant bone loss, which is believed to occur primarily through changes in trabecular and intracortical bone remodeling; and, postmenopausal women receiving estrogen therapy have higher BMD than those not receiving this treatment (45).

Moreover, prior studies reporting an association between BMD and colorectal cancer varied in terms of the other covariates included in their models – some authors used models adjusted only for age, gender, race and BMI while others adjusted for additional risk factors such as family history of colorectal cancer, smoking, alcohol, physical activity, NSAID use, etc. In our study, models including age, gender, race and BMI were similar to more fully adjusted models. Incorporating the additional risk factors improved the precision of effect estimates in some cases (e.g., in female total body BMD analyses) but the additional adjustment did not materially change the overall interpretation. This suggests that when taking into account only a few easily and reliably measurable attributes (age, gender, race, BMI), BMD may serve as an objective biomarker of colorectal adenomas.

The use of an objective, composite marker, such as BMD, as an additional mechanism to help identify patients who may benefit from earlier screening for colorectal adenomas (and cancer) may be particularly appealing for several reasons. First, calcium, vitamin D, estrogen and physical activity, which are known to affect BMD through complex biological and physiological interactions (24–26, 28, 46), have all been independently associated with colon adenomas and colon cancer, however, results have not been consistent across studies (9–12, 14, 15, 19–22). These inconsistencies may be due, in part, to problems with accurately quantifying lifetime or long-term exposure to dietary and lifestyle factors using self-report questionnaires and ‘snap-shots’ of serum biomarkers (35–37). Furthermore, although the exact underlying mechanisms are not currently known, calcium, vitamin D and estrogen have all been shown to modify levels of cell differentiation and apoptosis in the colon epithelium (16–18, 47). Moreover, methods used to screen for BMD are non-invasive and quite efficient, with a whole body DXA scan taking only approximately 10 to 15 minutes.

We note that two of the three previous studies only reported significant associations between BMD and colon cancer in women (39, 40); and, the one study that included men did not report results separately for males and females (38). In our study, we observed a dose-response between higher total body BMD tertiles and colorectal adenomas in women. The lack of a dose-response finding among men in our study may be due, in part, to the smaller amount of variation in BMD among men compared to women (total body BMD standard deviation (s.d.): 0.124 vs. 0.146 g/cm^2; pelvis BMD s.d.: 0.145 vs. 0.206 g/cm^2; spine BMD s.d.: 0.146 vs. 0.242 g/cm^2). Nevertheless, given our current and the previous findings, one could speculate that BMD may have greater substantive value in females, particularly of middle-to-older age, which, arguably, could be undergoing BMD screening for osteoporosis and fracture risk anyway. Interestingly, it has been reported that women have a substantially lower adenoma detection rate compared to men, which, as Roy and Bianchi (48) suggest,

may indicate a decreased efficacy for colonoscopy screening to prevent colorectal cancer in women compared to men. Although Roy and Bianchi (48) acknowledge that their appraisal of the literature is quite controversial, they contend that the current evidence is strong enough to provide "a plausible reason to investigate other biomarkers that may help protect against colon cancer in women". Perhaps, BMD, although non-specific, could serve as such a marker.

In our study population, female cases, on average, reported an earlier age at menopause compared to controls (Table 1). Although we confirmed menopause using serum FSH and E2, the age at menopause was obtained by self-report and, therefore, may be biased. However, the bias is most likely non-differential between cases and controls since the information was obtained prospectively (i.e., prior to the colonoscopy outcome). It is also possible that the lower mean age at menopause we observed in cases compared to controls may reflect some other underlying unmeasured systemic condition.

There are several limitations of our study. The most important limitation relates to our small sample size, which led to small cell counts and prohibited a separate evaluation of premenopausal women. In addition, a larger sample would help to more definitively determine if there is (or is not) a dose-response association between higher BMD and colorectal adenomas in men. Although we controlled for factors that may affect estrogen levels in our analysis (e.g., BMI, post-menopausal status, years of HRT use), the possibility of residual confounding by an unmeasured estrogen measure cannot be ruled out. In particular, we did not have information to evaluate how the specific type or classification of HRT drug (e.g. estrogen alone vs. estrogen and progesterone) might have affected results. However, excluding HRT users from the analyses did not materially change the results. Furthermore, we were not able to quantify BMD at the specific sites previously reported in colon cancer (femoral neck, Ward's triangle, trochanter, metacarpal cortical area) using our total body DXA scan; however, we did use surrogate areas (pelvis, spine) to attempt to evaluate regions of similar bone composition.

In conclusion, we observed, for the first time, an inverse association between higher levels of BMD and colorectal adenomas, which stratification by gender revealed was more pronounced in females even when HRT users were excluded. Although additional larger, prospective studies are needed, our results suggest that BMD may be a biomarker for colorectal cancer precursor lesions.

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Table 1

Characteristics of the Colorectal Adenomas Study Population

Characteristic	Cases	Controls
Sample Size	67	100
Age (years)	58.6 (7.9)	54.8 (7.4) *
Gender		
Males	41 (61.2%)	38 (38.0%)
Females	26 (38.8%)	62 (62.0%) *
Race		
Caucasians	42 (62.7%)	70 (70.0%)
African-Americans	25 (37.3%)	30 (30.0%)
BMI (kg/m^2)	30.3 (7.2)	29.4 (7.1)
Smoked	41 (61.2%)	48 (48.0%) †
Used Alcohol	45 (67.2%)	71 (71.0%)
Family History of Colon Cancer	14 (20.9%)	29 (29.0%)
NSAID**	6 (9.2%)	17 (17.0%)
Total Energy Intake (kcal/day)	2135.3 (1626.7)	2032.8 (890.1)
Calcium Dietary Intake (g/day)	952.5 (603.3)	1070.8 (542.2)
Vitamin D Dietary Intake (IU/day)	143.0 (117.5)	171.8 (129.6)
Calcium Supplements (g/day)	177.2 (294.4)	242.5 (396.3)
Vitamin D Supplements (IU/day)	171.5 (236.4)	195.0 (251.2)
Total Calcium Intake (g/day)	1129.7 (615.4)	1313.4 (650.5) †
Total Vitamin D Intake (IU/day)	314.5 (272.1)	366.8 (297.3)
Physical Activity (kJ/day)	2521.7 (1046.0)	2542.6 (1150.0)
Post-Menopausal Women	18 (75.0%)	39 (62.9%)
Age at Menopause (yrs)	42.5 (8.8)	46.7 (7.0) †
HRT Use in Post-Menopausal Women‡	8 (33.3%)	13 (32.5%)
Years HRT Use In Post-Menopausal Women‡	10.9 (6.3)	11.1 (8.0)
Follicle-Stimulating Hormone (FSH; mIU/mL) in Postmenopausal Women	70.1 (30.5)	68.1 (29.4)
Estrodial (E2; pg/mL) in Postmenopausal Women	22.1 (20.0)	18.1 (9.8)

* $p \leq 0.05$ for Chi-square test or t-test between cases and controls

† $0.05 < p \leq 0.10$ Chi-square test or t-test between cases and controls

** Non-steroidal anti-inflammatory drug (NSAID) use

‡ Hormone replacement therapy (HRT) use was only found in post-menopausal women

Table 2

Associations Between Bone Mineral Density (BMD) and Colorectal Adenomas

Skeletal Site BMD Tertile (T) (g/cm^2)	Model 1*			Skeletal Site BMD Tertile (T) (g/cm^2)	Model 2†		
	N	OR (95% CI) **	P		N	OR (95% CI) **	p
Total Body				**Total Body**			
T1: <1.167	24/33	1.00 (Referent)	-	T1: <1.169	20/29	1.00 (Referent)	-
T2:1.167–1.294	23/33	0.29 (0.10–0.84)	0.02	T2: 1.169–1.301	20/29	0.39 (0.13–1.03)	0.07
T3: >1.294	20/34	0.26 (0.08–0.80)	0.02 0.02‡	T3: >1.301	19/29	0.38 (0.12–1.11)	0.09 0.09‡
T3 & T2 vs. T1	43/67	0.28 (0.10–0.74)	0.01	T3 & T2 vs. T1	39/58	0.38 (0.14–0.99)	0.05
Pelvis				**Pelvis**			
T1: <1.001	26/33	1.00 (Referent)	-	T1: <0.998	21/29	1.00 (Referent)	-
T2: 1.001–1.162	24/33	0.61 (0.25–1.53)	0.29	T2: 0.998–1.167	21/29	0.67 (0.26–1.64)	0.42
T3: >1.162	17/34	0.38 (0.13–1.05)	0.06 0.06‡	T3: >1.167	17/29	0.42 (0.15–1.12)	0.10 0.10‡
T3 vs. T2 & T1	17/67	0.51 (0.22–1.20)	0.12	T3 vs. T2 & T1	38/58	0.56 (0.23–1.27)	0.20
Spine				**Spine**			
T1: <1.050	22/33	1.00 (Referent)	-	T1: <1.068	20/29	1.00 (Referent)	-
T2: 1.050–1.220	24/33	0.52 (0.19–1.36)	0.18	T2: 1.068–1.223	19/29	0.40 (0.14–1.05)	0.08
T3: >1.220	21/34	0.40 (0.13–1.10)	0.09 0.11‡	T3: >1.223	19/29	0.38 (0.12–1.10)	0.09 0.08‡
T2 & T3 vs. T1	45/67	0.47 (0.19–1.18)	0.11	T2 & T3 vs. T1	38/58	0.39 (0.14–1.02)	0.06

*Adjusted for age, race, gender, BMI, smoking, alcohol, family history of colon cancer, NSAIDs, physical activity, total calcium, total Vitamin D, total energy intake

†Excludes HRT users and is adjusted for all variables listed above in *.

**Odds Ratio (OR) and 95% Confidence Interval (CI) of OR

‡p-value for trend

Table 3

Associations Between Bone Mineral Density (BMD) and Colorectal Adenomas: Females Only

Skeletal Site BMD Tertile (T) (g/cm^2)	Model 1* N	Model 1* OR (95% CI) **	Model 1* p	Skeletal Site BMD Tertile (T) (g/cm^2)	Model 2† N	Model 2† OR (95% CI) **	Model 2† p
Total Body				**Total Body**			
T1: <1.130	13/20	1.00 (Referent)	-	T1: <1.132	9/16	1.00 (Referent)	-
T2:1.130–1.280	5/20	0.15 (0.04–0.94)	0.04	T2: 1.132–1.295	4/16	0.16 (0.02–1.03)	0.07
T3: >1.280	8/21	0.08 (0.01–0.70)	0.02 0.02‡	T3: >1.295	5/16	0.06 (0.01–0.75)	0.03 0.04‡
T2 & T3 vs. T1	13/61	0.13 (0.03–0.70)	0.02	T3 & T2 vs. T1	9/22	0.17 (0.03–0.97)	0.04
Pelvis				**Pelvis**			
T1: <0.980	13/20	1.00 (Referent)	-	T1: <0.980	9/16	1.00 (Referent)	-
T2: 0.980–1.123	6/21	0.15 (0.04–0.95)	0.04	T2: 0.980–1.156	5/16	0.25 (0.04–1.24)	0.14
T3: >1.123	7/20	0.12 (0.02–1.00)	0.05 0.04‡	T3: >1.156	4/16	0.13 (0.01–1.03)	0.07 0.07‡
T2 & T3 vs. T1	13/61	0.14 (0.03–0.73)	0.02	T3 vs. T2 & T1	9/22	0.21 (0.03–1.08)	0.09
Spine				**Spine**			
T1: <1.017	13/20	1.00 (Referent)	-	T1: <1.018	9/16	1.00 (Referent)	-
T2: 1.017–1.209	6/20	0.12 (0.02–0.72)	0.02	T2: 1.018–1.220	4/16	0.09 (0.01–0.69)	0.02
T3: >1.209	7/21	0.04 (0.01–0.45)	0.01 0.01‡	T3: >1.220	5/16	0.04 (0.01–0.56)	0.01 0.01‡
T2 & T3 vs. T1	13/61	0.09 (0.02–0.51)	0.01	T2 & T3 vs. T1	9/22	0.07 (0.01–0.52)	0.01

*Adjusted for age, race, gender, BMI, smoking, alcohol, family history of colon cancer, NSAIDs, physical activity, total calcium, total Vitamin D, total energy intake, menopausal status, age at menopause, years of HRT use

†Excludes HRT users. Adjusted for all variables listed above in * except years of HRT use

**Odds Ratio (OR) and 95% Confidence Interval (CI) of OR

‡p-value for trend

Table 4

Associations Between BMD and Colorectal Adenomas: Males Only

Skeletal Site BMD Tertile (T) (g/cm^2)	N	Model 1*	
		OR (95% CI)†	p
Total Body			
T1: <1.233	19/12	1.00 (Referent)	-
T2:1.233–1.312	9/13	0.23 (0.05–0.98)	0.05
T3: >1.312	13/13	0.34 (0.08–1.36)	0.16
			0.10**
T2 & T3 vs. T1	13/38	0.34 (0.11–1.07)	0.07
Pelvis			
T1: <1.026	15/12	1.00 (Referent)	-
T2: 1.026–1.172	14/13	0.67 (0.19–2.43)	0.55
T3: >1.172	12/13	0.64 (0.17–2.41)	0.51
			0.51**
T2 & T3 vs. T1	41/38	0.66 (0.21–2.05)	0.47
Spine			
T1: <1.105	16/12	1.00 (Referent)	-
T2: 1.105–1.263	15/13	0.63 (0.18–2.21)	0.47
T3: >1.263	10/13	0.25 (0.06–1.03)	0.06
			0.06**
T2 vs. T3 & T1	45/67	0.32 (0.10–1.09)	0.07

*Adjusted for age, race, gender, BMI, smoking, alcohol, family history of colon cancer, NSAIDs, physical activity, total calcium, total Vitamin D, total energy intake

†Odds Ratio (OR) and 95% Confidence Interval (CI) of OR

**p-value for trend