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Bone mineral density and the subsequent risk of cancer in the NHANES I follow-up cohort

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Abstract

Backgroud: Bone mineral density (BMD) is a marker of long-term estrogen exposure. BMD measurement has been used in this context to investigate the association of estrogen with breast cancer risk in three cohorts. In order to assess further BMD as a predictor of estrogen related cancer risk, the association of BMD with colorectal and corpus uteri cancer was investigated in the NHANES I Epidemiologic Followup Study (NHEFS) cohort along with breast cancer and prostate cancer.

Methods: Participants were members of the NHEFS cohort who had BMD measurement in 1974–1975. Age, race, and BMI adjusted rate ratios and 95% confidence intervals were calculated for incidence of cancers of the corpus uterus, breast, colorectum, prostate, and of osteoporosis and hip fracture related to baseline BMD.

Results: Data were available for 6046 individuals. One hundred cases of breast cancer, 94 prostate cancers, 115 colorectal cancers, 29 uterine cancers, 110 cases of hip fracture and 103 cases of osteoporosis were reported between 1974 and 1993. Hip fracture and osteoporosis were both significantly inversely associated with BMD. Uterine cancer was positively associated ($p = 0.005$, test for linear trend) and colorectal cancer negatively associated ($p = 0.03$) with BMD. No association was found between elevated BMD and incidence of breast cancer ($p = 0.74$) or prostate cancer ($p = 0.37$) in the overall cohort, although a weak association was seen between BMD and subsequent breast cancer incidence when BMD was measured in post-menopausal women ($p = 0.04$).

Conclusion: The findings related to cancers of the uterus and colorectum as well as the weak association of BMD with breast cancer strengthen the use of BMD as a marker of estrogen exposure and cancer risk.

Background

Three recent reports, from the Study of Osteoporotic Fractures [1], Framingham [2], and the Fracture Intervention Trial [3] demonstrated a positive association between bone mineral density measurements (BMD) in women and subsequent onset of breast cancer. All of these reports were regarded as significant because estrogen has been thought to increase breast cancer risk [4] and BMD may be a more accurate measure of long term estrogen exposure than recall of hormone supplementation, measurements of endogenous estrogen, parity, or obesity [5,6].

In the light of strong associations previously noted between estrogens and corpus uteri cancer, BMD should predict the occurrence of endometrial cancer [4], though this has not yet been directly assessed. BMD also reflects exposure to calcium and to physical activity as well as foods affecting calcium absorption and deposition [7–9]. All of these factors, including estrogen, are thought to diminish the risk of colorectal cancer [10,11]. On the other hand increased calcium intake has been associated with increased risk of prostate cancer [12,13]. Because of the intimate association of BMD with to all of these exposure variables, BMD needs to be examined in relation to each of these cancers. In this report we use the NHANES I Epidemiological Followup Study to pursue four hypotheses relating BMD to cancer: that BMD will correlate directly with subsequent breast, uterus, and prostate cancer incidence, and that BMD will correlate inversely with subsequent colorectal cancer incidence.

Methods

The First National Health and Nutrition Examination Survey (NHANES I) collected data from a national probability sample of the United States civilian noninstitutionalized population between the ages of one and seventy-four years [14]. The initial survey took place from 1971 through 1974. In addition to the emphasis on nutrition in NHANES I, a subset sample of persons age 25–74 received a more detailed health examination through October 1975. This additional exam included a hand/wrist x-ray. This was successfully completed in 6, 413 subjects. Each x-ray was a posterior/anterior view of the left hand and wrist taken by direct exposure using 10 × 12 Eastman Industrial Type AA "Ready Pak" film. The prescribed radiography technique called for a focus to film distance of 36 inches with the focal spot centered on the midpoint of the third metacarpal. These hand/wrist x-rays were originally evaluated for BMD by photo densitometry measurements of the phalanx V-2 and the radius. BMD was determined from the radiography using a reference wedge. The hand/wrist x-rays have since been reread for bone density using a technique called Osteo Gram Radiographic Absorptiometry (RA) by Compu-Med Incorporated. BMD could not be calculated using this method for 153 of the 6, 413 subjects with hand x-rays due to improper exposure, poor picture quality, damaged or missing film. Records for the 6, 260 cases that have been reread are contained in the Public Use File (Radiography Absorptiometry Bone Density). Additional data on RA can be found in an introduction to that public use file. RA has been found to have an excellent precision (CV of 0.6%) and accuracy and to correlate well with other accepted methods of bone densitometry.

Data on disease incidence were obtained on the individuals from the NHANES I Epidemiologic Followup Studies (NHEFS), which was conducted in four waves of data collection through 1993. Data collected included in depth interviews with subjects or their proxies, hospital records, including pathology reports, and collection of death certificates for deceased subjects. Tracing is complete for 90% of the cohort through 1993.

Those with at least one follow-up record in NHEFS were included in the analysis, resulting in a final sample size of 6,046. Disease outcomes were obtained using ICD-9 codes (International Classification of Diseases, 9th Revision) from death certificates and hospital record diagnostic codes in NHEFS mortality and health care facility stay data bases, respectively. They were: uterine cancer (179, 182.0, 182.1, 182.8), colorectal cancer (153.0–154.3, 154.8), breast cancer (174.0–174.9), prostate cancer (185), hip fractures (820.0–820.3, 820.8, 820.9), and osteoporosis (733.00–733.03, 733.09).

Person-years of follow-up were computed for each cohort as the amount of time since the NHANES I examination to the date of the first of the following events: date of ICD-9 disease code of interest from the health care facility stay files, date of death from the NHEFS mortality file, or the last day of contact from the 1992 NHEFS vital status file. Thus, subjects were right-censored at either death or last date of follow-up. For persons with more than one hospital admission listing a particular disease outcome of interest, the date of the earliest admission for that disease was used. Person-years of follow-up were calculated separately for each disease outcome. Cohorts who reported at baseline a history of hip fracture were excluded from the hip fracture analysis (30 women and 27 men) for a total sample size of 5989, and those who reported a prior malignant tumor or growth were excluded from the cancer analyses (120 women and 49 men) for total sample sizes of 5877 for the colorectal cancer analysis, 3108 women for the breast and uterine cancer analyses, and 2769 men for the prostate cancer analysis.

Cohorts were divided into 4 groups according to their RA BMD: <95, 95–105, 105–115, >115 (mass/volume units established by Compu-Med). Chi square tests for trend

Table 1: Characteristics of study participants by bone mass density

	Number	Mean (SD) Age (years)	Mean (SD) BMI (kg/m^2)	Proportion Caucasian	Proportion Male
ALL PARTICIPANTS					
All BMD	6046	48.9 (14.1)	25.7 (5.1)	86.9	46.6
BMD <95	1607	60.7 (9.9)	25.8 (5.0)	87.0	41.6
BMD 95–105	1363	50.3 (13.3)	25.9 (5.2)	89.4	51.1
BMD 105–115	1491	43.8 (12.5)	25.6 (5.1)	87.0	49.8
BMD >115	1585	40.5 (11.1)	25.5 (5.0)	84.4	44.8
p-value for BMD trend		0.0001	0.07	0.009	0.10
MALES					
All BMD	2818	49.3 (14.1)	25.8 (4.2)	87.0	
BMD <95	668	59.4 (10.8)	25.4 (4.4)	87.1	
BMD 95–105	697	51.6 (13.4)	25.7 (4.1)	88.8	
BMD 105–115	743	45.4 (13.0)	25.9 (4.3)	86.7	
BMD >115	710	41.6 (12.3)	26.1 (4.1)	85.5	
p-value for BMD trend		0.0001	0.001	0.21	
FEMALES					
All BMD	3228	48.5 (14.1)	25.6 (5.7)	86.7	
BMD <95	939	61.5 (9.2)	26.1 (5.3)	86.9	
BMD 95–105	666	48.8 (13.1)	26.0 (6.2)	90.1	
BMD 105–115	748	42.3 (11.8)	25.4 (5.7)	87.3	
BMD >115	875	39.7 (9.9)	25.1 (5.6)	83.5	
p-value for BMD trend		0.0001	0.0001	0.02	
FEMALES > 55 YEARS					
All BMD	1162	64.0 (5.6)	26.9 (5.6)	86.4	
BMD <80.3	288	66.5 (5.2)	25.8 (5.2)	88.9	
BMD 80.3–89.7	289	64.8 (5.5)	26.7 (5.4)	85.8	
BMD 89.7–99.9	291	63.3 (5.5)	27.1 (5.3)	88.7	
BMD >99.9	294	61.7 (5.1)	28.2 (6.4)	87.3	
p-value for BMD trend		0.0001	0.0001	0.06	

BMI; Body Mass Index. BMD; Bone Mineral Density. Two males and 1 female had missing values for BMI. P-values for BMD trend from linear regression analysis with single indicator variable for BMD (age, BMI) and Mantel-Hansel Chi-square test for trend (race, gender).

and linear regression analysis using a single variable for RA-BMD group were used to evaluate the relationship of BMD to BMI, gender, age and ethnicity, as appropriate. For each diagnosis of interest, incidence rates were calculated for each BMD group by dividing the number of cases of disease by the number of person-years of follow-up. Cox proportional-hazards models were fitted for disease outcomes with BMD groups using the PHREG procedure from the SAS System for Windows Version 8.01. Covariates in the analysis were age at NHANES I examination (<35, 35–50, 50–60, and >60 years), body mass index (BMI; weight in kg/height in m^2) at NHANES I examination (<22, 22–25, 25–28, >28), and race (Caucasian versus other). Analyses of colorectal cancer, hip fractures and osteoporosis outcomes were adjusted for gender. Similar models, replacing the 3 indicator variables for RA BMD with a single variable for RA BMD group, were tested to determine the significance of the trend in risk of disease. For the analysis including only women older than 55 years, the cohort was divided into 4 groups according to BMD quartile. The association of BMD quartile with breast cancer in women older than 55 was tested using Cox proportional hazards models as described above. Covariates included in the model were indicator variables for quartile of age, quartile of BMI, and race (Caucasian versus other). Since we would expect that age would be exponentially related to cancer, and for breast and uterine cancer the slope of the exponential line would change after menopause, the use of age categories did not constrain age to be linearly related to the outcome.

Results

The BMD sample of NHANES I included 6, 046 individuals who had bone density read by RA and follow-up data in NHEFS. This group included 5, 252 Caucasians, 742 African Americans, and 52 individuals of Hispanic origin. There were 2, 818 men and 3, 228 women. The median age at the time of bone density reading was slightly less than 50 years. Table 1 describes the relationship of gender

and race to age, body mass index, and BMD within the cohort.

Table 2: Bone mineral density and subsequent incidence of osteoporosis and hip fracture in men and women

	Number in Cohort	Number of Cases	Incidence Rate (cases/100 person years)	Age, Gender, Race & BMI Adjusted Rate Ratio (95% CI)	p-value for rate ratio
Hip Fractures					
All	5989	110	1.14		
RA BMD					
<95	1577	74	3.36	1	
95–105	1352	21	0.96	0.57 (0.34–0.93)	P = 0.03
105–115	1483	8	0.32	0.33 (0.15–0.71)	P = 0.005
>115	1577	7	0.26	0.36 (0.15–0.83)	P = 0.02
Test for Linear Trend					P = 0.0005
Osteoporosis					
All	6046	103	1.06		
RA BMD					
<95	1607	70	3.13	1	
95–105	1363	17	0.77	0.53 (0.31–0.91)	P = 0.02
105–115	1491	8	0.32	0.38 (0.18–0.83)	P = 0.02
>115	1585	8	0.29	0.42 (0.19–0.95)	P = 0.04
Test for Linear Trend					P = 0.003

BMI; Body Mass Index. RA BMD; Bone Mineral Density by Radioabsorbimetry

Table 3: Bone mineral density and subsequent incidence of uterine cancer

	Number in Cohort	Number of Cases	Incidence Rate (cases/100 person years)	Age, Race & BMI Adjusted Rate Ratio (95% CI)	p-value for rate ratio
Uterine Cancer					
All	3108	26	0.50		
RA BMD					
<95	890	7	0.52	1	
95–105	635	5	0.46	1.56 (0.48–5.05)	P = 0.46
105–115	725	5	0.40	2.44 (0.71–8.33)	P = 0.15
>115	858	9	0.60	5.01 (1.61–15.62)	P = 0.006
Test for Linear Trend					P = 0.005

BMI; Body Mass Index. RA BMD; Bone Mineral Density by Radioabsorbimetry

By 1993, a total of 103 cases of osteoporosis, 110 cases of reported hip fracture, 115 cases of colorectal cancer, 100 cases of breast cancer, 94 cases of prostate cancer and 26 cases of uterine cancer had been reported within this subset of the NHANES I cohort. Significant inverse associations were seen with both osteoporosis and hip fracture (Table 2) after adjustment for age, BMI, race, and gender.

Table 3 describes the relationship of BMD to uterine cancer risk. After age, race and BMI adjustment there was a significant (p = 0.005) trend to increasing risk with increasing BMD.

A trend was not seen between BMD and the subsequent incidence of breast cancer in the overall cohort (Table 4: p = 0.74). However, in women who were over the age of 55

Table 4: Bone mineral density and subsequent incidence of breast cancer

	Number in Cohort	Number of Cases	Incidence Rate (cases/100 person years)	Age, Race & BMI Adjusted Rate Ratio (95% CI)	p-value for rate ratio
Breast Cancer (all Women)					
All	3108	100	1.94		
RA BMD					
<95	890	26	1.95	1	
95–105	635	35	3.26	2.19 (1.27–3.77)	P = 0.005
105–115	635	15	1.19	1.00 (0.49–2.020	P = 0.99
>115	858	24	1.60	1.45 (0.75–2.82)	P = 0.27
Test for Linear Trend					P = 0.74
Breast Cancer (Women over 55 Years Old)					
All	1091	43	2.68		
RA BMD					
<80.3	272	10	2.71	1	
80.3–89.7	273	2	0.49	0.19 (0.04–0.88)	P = 0.03
89.7–99.9	273	16	3.90	1.65 (0.73–3.75)	P = 0.23
>99.9	273	15	3.59	1.66 (0.69–3.99)	P = 0.26
Test for Linear Trend					P = 0.04

BMI; Body Mass Index. RA BMD; Bone Mineral Density by Radioabsorbimetry For the analysis of breast cancer in women over 55 years of age, indicator variables were created for quartiles of RA BMD, age, and BMI.

Table 5: Bone mineral density and subsequent incidence of colorectal cancer

	Number in Cohort	Number of Cases	Incidence Rate (cases/100 person years)	Age, Gender, Race & BMI Adjusted Rate Ratio (95% CI)	p-value for rate ratio
Colorectal Cancer					
All	5877	115	1.21		
RA BMD					
<95	1539	58	2.67	1	
95–105	1321	30	1.40	0.84 (0.53–1.31)	P = 0.44
105–115	1459	16	0.65	0.63 (0.35–1.13)	P = 0.12
>115	1558	11	0.41	0.52 (0.26–1.04)	P = 0.06
Test for Linear Trend					P = 0.03

BMI; Body Mass Index. RA BMD; Bone Mineral Density by Radioabsorbimetry

(n = 1091), that is, probably after the age of menopause at the time that their BMD was measured, a positive association of BMD and breast cancer was suggested (p = 0.04 for trend in a quartile comparison). A total of 43 breast cancers developed in this latter, older group.

There was an inverse association of BMD with colorectal cancer after adjustment for age, race, BMI, and gender that was statistically significance (p = 0.03: Table 5).

Prostate cancer risk was not significantly associated with increasing levels of BMD (p = 0.37), although there were diminished risks in upper quartiles of BMD, which was in the opposite direction of our hypothesis (Table 6).

Discussion

Hip fracture and osteoporosis

As in the Framingham cohort, the choice of bone for BMD measurement in NHANES I was the metacarpal [2]. Much has been written about the optimal choice of bone for

Table 6: Bone mineral density and subsequent incidence of prostate cancer

	Number in Cohort	Number of Cases	Incidence Rate (cases/100 person years)	Age, Race & BMI Adjusted Rate Ratio (95% CI)	p-value for rate ratio
Prostate; Men					
All	2769	94	2.20		
RA BMD					
<95	649	39	4.68	1	
95–105	686	22	2.09	0.63 (0.37–1.07)	P = 0.09
105–115	734	20	1.67	0.86 (0.49–1.49)	P = 0.59
>115	700	13	1.10	0.72 (0.38–1.38)	P = 0.32
Test for Linear Trend					P = 0.37

BMI; Body Mass Index. RA BMD; Bone Mineral Density by Radioabsorbimetry

BMD measurement, though no clear preference has dominated this literature [15–17]. Because we assumed that the most direct consequences of diminished BMD would be osteoporosis and hip fracture, associations of BMD with hip fracture and the development of osteoporosis were investigated in order to establish the validity of this BMD measurement in this cohort. As anticipated, in the NHEFS, diminished BMD is significantly associated with the development of osteoporosis and hip fracture (Table 2).

Uterine cancer

This is the first report that examines the relationship of BMD to uterine cancer. Because the association of estrogen exposure and uterine cancer development is far less controversial than estrogen and breast cancer risk [4], the veracity of BMD as a measure of estrogen exposure is supported by the significant positive association of BMD with uterine cancer incidence (Table 3).

Breast cancer

Although no association between BMD and subsequent breast cancer incidence was found for all women in the cohort, a weak but significant association was seen in those over 55 years of age at the time of BMD measurement, i.e. post menopause. The total number of breast cancer cases is comparable to the three studies discussed below, as is the size of the cohort. However, the three previous studies all recruited peri- and post-menopausal women [1–3], an age group that comprised just less than half the women in the NHANES I BMD cohort. The NHANES I female BMD cohort size and number of breast cancer cases in this post-menopausal subgroup are therefore smaller than the other studies. Nevertheless, there is a significant, though unstable trend towards increasing breast cancer risk with rising BMD in those women recruited to NHANES I older than 55 years (Table 4).

The relationship of estrogen exposure to subsequent breast cancer risk has been the subject of much debate and investigation [4]. The debate is all the more significant because of estrogen's possible role in the prevention of coronary heart disease mortality, hip fracture and osteoporosis [5]. Three studies were greeted with great enthusiasm because they added a new perspective to the debate, correlating BMD with breast cancer risk. In so doing they seemed to confirm that estrogen exposure over a long period of time increased the risk of breast cancer [1–3], (Table 7). In the Study of Osteoporotic Fractures, 6, 854 women greater than 65 years old had their BMD measured and were followed-up for an average of 3.2 years. Ninety-seven women developed breast cancer [1]. The incidence rate of breast cancer varied from 2.46 cases / 1000 person years in the lowest quartile of bone mineral density to 5.99 cases / 1000 person years in the highest quartile (relative risk 1.50: 95% confidence interval = 1.16 to 1.95).

In the Framingham study, 1, 373 women age 47 to 80 years had bone density measured from 1967 to 1970. By 1993, 91 women developed breast cancer [2]. The age adjusted rate ratios for breast cancer from the lowest to the highest quartile of BMD were 1.0, 1.3, 1.3 and 1.5 respectively. However, the effect was found to be far greater in women with a positive family history of breast cancer in the Framingham report. Among those without a family history of breast cancer, the risk was not significantly increased [18].

In the Fracture Intervention Trial, 8203 postmenopausal women between 54 and 80 years of age were enrolled in a therapeutic trial related to fracture prevention [3]. With a maximum of five years of follow-up, a total of 158 women were found to have breast cancer, 131 of which received the diagnosis more than six months after enrollment, and 102 of which were invasive cancers. Treatment (alendro-

Table 7: Bone mineral density and breast cancer risk

Cohort; Size	BMD Measure	Cases	Significant Association Breast	Uterus Also Assessed?	Significant Association Uterus
SOF 9704	DEXA; Radius, Hip, Calcaneus	97	Yes; Positive	No	
Framingham 1373	RG Metacarpal	91	Yes* Positive	No	
FIT 8203	DEXA Femur	102	Yes; Positive	No	
NHANES-1 6046	RA Metacarpal	100	Yes: post meno pausal only	Yes; 29 cases	Yes; Positive
Sweden 18,000 Hip Fractures	Hip Fracture prior to cancer diagnosis	253	Yes; Inverse@	Yes; 55 cases	No
Sweden 9673 Breast Cancers	Hip Fracture after breast cancer diagnosis	387 Hip Fractures	No	Yes; 2111 cases	Yes; Inverse@
Sweden 677 Forearm Fractures	Forearm fracture	11 cases Breast Cancer	Yes; Inverse@	Yes; 5 cases	Yes; Inverse@
Rochester, MN Case/Control 235 Breast Cancers	Osteoporotic Fracture before & after cancer diagnosis		No	No	
US Multistate Tumor Registry; Case/Control 5559 Breast Cancers & 739 Uterine Cancers	Past Fracture before cancer diagnosis	352 Fractures < or = 5 years prior to Breast Cancer Diagnosis	Yes; Inverse@	Yes; 35 Fractures	Yes; Inverse@

SOF; Study of Osteoporotic Fractures FIT; Fracture Intervention Trial DEXA; Dual Energy X-ray Absorbimetry RA; Radioabsorbimitry RG; Radiogramimetry *; The strongest association was in those women with positive family histories for breast cancer. @; A significant inverse association in the fracture trials is equivalent to a positive association in BMD trials.

nate for osteoporosis) in the randomized trial did not alter breast cancer risk. Age adjusted risk increased with increasing quartiles of BMD, though marginal statistical significance was achieved for invasive cancer only in the highest versus lowest BMD quartiles (OR = 1.8; 95% CI = 1.0–3.2). Unlike Framingham, family history of breast cancer did not alter the results related to BMD. Calcium and vitamin D ingestion were found to be associated with diminished breast cancer risk. This might imply that the estrogen effect on breast cancer risk, as manifested in BMD, could have been diminished by increasing exposure to calcium and vitamin D.

An indirect method has been employed to assess the relationship of estrogen exposure to breast cancer risk through bone density assessment: the association of osteoporotic fracture to the prior or subsequent diagnosis of breast and uterine cancer (Table 7). One recent large case/control study presents compelling evidence for diminished risk of previous recent fracture in women with both breast and uterine cancer [19]. Four earlier reports of fracture and breast cancer were evenly divided in their results, though the negative studies included fracture after the diagnosis of cancer [20,21,23,24]. Uterine cancer has also been assessed in all but one of these reports [20,22,23] and found to be positively associated with fracture in two.

Colorectal cancer

The results of these analyses show a protective trend of BMD for colorectal cancer that is statistically significant (Table 5). Estrogen is thought to diminish risk for colorectal cancer, though there has been variation in findings concerning which subsite within the colorectum is protected by estrogen exposure. Other factors related to BMD are also thought to effect colorectal cancer risk, positively (age, body mass index, smoking) or negatively (calcium, estrogen, physical activity) [9,10]. Of these, the most widely investigated has been calcium. Twenty-four analytic studies of calcium in cohort and case/control designs have been reported. Only ten of these have shown a significant decrease in colon cancer risk associated with calcium intake. In addition, there have been 8 studies of vitamin D intake, only 3 of which have shown decreased colorectal cancer risk related to increased vitamin D [25].

The reason for these inconsistent results relating to calcium may be that calcium nutriture is difficult to measure. Bioavailability of calcium is related to the intake of other nutrients, which include dietary fiber (phytate), phosphate, alcohol, and tea (tannins). Each can alter colorectal cancer risk. Therefore, serum calcium levels and dietary intake do not necessarily reflect endogenous content. As with iron, endogenous calcium stores may be the more

significant effector of risk than dietary calcium intake [26]. In the case of calcium, the measure of endogenous stores is BMD.

The investigation of BMD and colorectal cancer risk, therefore, provides a new perspective in the analysis of calcium and colorectal cancer risk, and in addition provides information on two other factors for colorectal cancer that are thought to diminish risk: physical activity and estrogen [10]. This is the first such report analyzing this association.

Prostatic cancer

Reported herein is the first study to obtain BMD measurement prior to the diagnosis of prostate cancer, and no association was found (Table 6). Calcium ingestion has also been associated with increased risk of prostate cancer [10,11]. The only study to look at BMD and prostate cancer risk was a case/control design. It showed no association, although cases already had prostate cancer when BMD was measured and controls were patients with other urologic diseases or presenting for prostate cancer screening [27].

BMD and estrogen

BMD is affected by many factors other than estrogen, including principally age, calcium, body mass index, cigarette smoking, physical activity, and prior bone injury. As such it is a non-specific indicator of risk. BMD was also measured in NHANES I at a time when post-menopausal use of estrogen was rare. Its increasing use in recent decades may have altered the subsequent risk of cancer in these women. Nevertheless, the results seen in opposite directions in uterus and colorectum suggest that estrogen exposure at least up to the point at which BMD was measured was a significant mediator of risk for cancer in NHANES I. The weakly positive results for breast cancer in combination with previously published reports suggest that, unlike the other endpoints reported herein, BMD as a predictor of breast cancer risk is only of use when measured after menopause.

Conclusions

In summary, this NHANES I cohort follow-up is the first report of analyses of BMD and subsequent risk for cancer of the colorectum and uterus, the fourth for breast cancer risk and the second for prostate cancer. A strong positive association was seen between BMD and corpus uteri cancer, and a significant trend towards decreasing colorectal cancer risk with increasing BMD. There is an insignificant decline in risk for prostate cancer with increasing BMD, a direction opposite of our initial hypothesis. A weak relationship could be detected between breast cancer and BMD only when BMD was measured after menopause. Significant inverse associations were found between BMD, osteoporosis and hip fracture.

Competing interests

None declared

Author's Contributions

R. Nelson; Conceived the study, wrote the paper, reviewed relevant literature. V. Persky; Provided overall epidemiologic expertise and guidance. M. Turyk & J. Kim; Accessed NHANES tapes, downloaded data and performed statistical analyses and wrote most of the methods sections. All authors reviewed the manuscript and contributed to it.

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