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Serum calcium and incident and fatal prostate cancer in the National Health and Nutrition Examination Survey

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Abstract

We examined the association between serum calcium levels and the risk for prostate cancer using a prospective cohort, the National Health and Nutrition Examination Survey (NHANES) and the NHANES Epidemiologic Follow-up Study (NHEFS). Eighty five incident cases of prostate cancer and twenty five prostate cancer deaths occurred over 46,188 person-years of follow-up. Serum calcium was determined an average of 9.9 years prior to the diagnosis of prostate cancer. Comparing men in the top to men in the bottom tertile of serum calcium, the multivariable adjusted relative hazard for fatal prostate cancers was 2.68 (95% Confidence Interval 1.02-6.99; P_{trend} = 0.04). For incident prostate cancer, the relative risk for the same comparison was 1.31 (95% C.I. 0.77-2.20; P_{trend}=0.34). These results support the hypothesis that high serum calcium or a factor strongly associated with it, e.g., high serum parathyroid hormone, increases risk for fatal prostate cancer. Our finding of a > 2.5- fold increased risk for men in the highest tertile of serum calcium is comparable in magnitude to the risk associated with family history and could add significantly to our ability to identify men at increased risk for fatal prostate cancer.

Little is known conclusively about the etiology of prostate cancer, which is the second leading cause of cancer deaths among U.S. men (1). We recently proposed that high serum levels of parathyroid hormone (PTH) increase the risk of advanced prostate cancer (2). Under normal physiologic conditions, serum PTH acts to maintain serum calcium levels within a narrow range (~ 9-10.5 mg/dl). However, prostate cancer cells express receptors for PTH (PTH-Type I receptors) and for calcium (calcium-sensing receptors) (3). In laboratory studies, PTH and calcium each promote the growth and metastasis of prostate cancer cells (4) (5). These observations led us to ask whether men with high levels of serum calcium are at increased risk for prostate cancer.

METHODS

We conducted a prospective cohort study of serum calcium and risk for incident and fatal prostate cancer using the first National Health and Nutrition Examination Survey (NHANES) and the NHANES Epidemiologic Follow-up Study (6-9). We included males aged 24 to 77 years at baseline examination in 1971 – 1975. Participants who reported lung, colon, or prostate cancers prior to the baseline exam (n=102) and those who reported prostate cancer or died within one year of baseline (n=90) were excluded. The final analytical cohort included 2,814 men for whom baseline serum calcium measurements were available.

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Person-time at risk was calculated as the interval between the dates of initial examination and prostate cancer diagnosis or death (for cases) or date of last contact (for non-cases). Prostate cancer was ascertained by self-report (with or without a recorded hospital stay) and by death certificate. Cases with a death record were considered fatal cases, and all others were considered non-fatal cases. For cases with a hospital record, the date of diagnosis was the date of first admission for prostate cancer. For cases without hospital record the diagnosis date was defined as June 30 of the year of self-report. For cases confirmed by death certificate only, the date of diagnosis was the date of death. The earliest diagnosis date was used for cases with multiple dates. Fatal cases were identified through death record linkage with 'prostate cancer' mentioned as a cause of death.

We estimated relative risks using Cox proportional hazards models relating tertiles of serum calcium to prostate cancer while controlling for potential confounders. Potential confounding was evaluated by age (years), BMI (as both a continuous and a categorical variable, cut point at 25 kg/m^2), race (black or white) and self-reported family history of prostate cancer. Linear trend was modeled as the median serum calcium value for each tertile as a continuous value. Statistical interaction was tested by likelihood ratio test of saturated models and Wald's test of cross-product terms. Analyses were performed using SAS 9.1 (SAS Inc., Carey, NC).

RESULTS

Eighty-five incident cases of prostate cancer, including 25 fatal cases, were observed among 2,814 men over 46,188 person-years of follow-up (1971 – 1993). The 25 fatal cases included 10 cases for which the death certificate was the only record of prostate cancer. Men with higher serum calcium tended to be younger (46 versus 52 years in the 3rd and 1st tertiles respectively), and were more likely to be black (15.4% versus 11.6% black in the 3rd and 1st tertiles).

There was no evidence of increased risk of incident disease with increasing serum calcium levels. Conversely, comparing men in the top to men in the bottom tertile of serum calcium, we observed a significantly increased hazard for fatal prostate cancer that persisted after adjustment for age (age-adjusted relative hazard of 2.59 (95% Confidence Interval, 1.00 - 6.72; P_{trend} = 0.05), BMI (age-and BMI-adjusted relative hazard = 2.62, Confidence Interval 1.01-6.80; P_{trend} = 0.04) and race (age- and BMI- and race- adjusted relative hazard = 2.68 (95% Confidence Interval 1.02-6.99; P_{trend} = 0.04). Tests for linear trend were statistically significant. However, most of the excess risk was concentrated in the top tertile of serum calcium. There was no substantive difference between adjusting for BMI as a continuous or categorical variable. Adjustment for family history of prostate cancer did not alter the point estimate but widened the confidence interval (P_{trend}= 0.06). We did not detect statistically significant interactions between serum calcium and other major risk factors for prostate cancer, but power was limited.

DISCUSSION

In this prospective cohort, we observed an approximately 3-fold increased risk for fatal prostate cancer among men in the upper tertile of the distribution of serum calcium. We observed a significant dose-response. To our knowledge, this is the first study to examine prostate cancer risk in relation to serum calcium. The measurement of serum calcium preceded the diagnosis of prostate cancer by an average of 9.9 years (SD = 4.5 years).

Numerous studies have investigated the role of dietary calcium in prostate cancer, with mixed results (e.g., 10-12). Calcium levels in serum are tightly controlled over a wide range of dietary calcium and generally are not correlated with dietary calcium levels (13). For example, in a random subsample of 354 subjects drawn from a cross sectional study of > 3,400 participants,

Mataix et al. found no relationship between measurements of calcium in the diet and in serum (14). The concentration of serum ionized calcium, the biologically active fraction of calcium, is tightly regulated by PTH and normally does not deviate by more that 2% from its set point. This contributes to the stability of total serum calcium levels, of which approximately 50% is ionized (15).

High serum calcium significantly predicted fatal but not incident prostate cancer. This may reflect the fact that in the "post-PSA era", incident prostate cancers are predominantly screen-detected cancers that are not life-threatening (i.e., are not true cases). Additionally, some self-reported cases of prostate cancer may have been missed (i.e. under-reporting) and some may have been mis-reported (i.e. over-reporting). This form of misclassification is likely to be non-differential and therefore bias results toward the null. Our finding is consistent with the results of a large population-based study of serum calcium and survival. In that study of 33,346 Swedes, Liefsson and Ahrén found an increased risk for fatal (cause not further specified) but not for incident malignancy among men less than 50 years of age with serum calcium > 2.5 mmol/L (10.0 mg/dl) (16). It is noteworthy that the increased cancer mortality observed in this Swedish study was observed for men with serum calcium in the upper, but normal reference range.

The normal range for serum calcium varies by laboratory and by assay methods. A commonly used reference range is 9-10.5 mg/dl (2.10 – 2.50 mmol/L) (17). Few cases in our study were hypercalcemic (2/25 = 8% had serum calcium > 10.5 mg/dl). Rather, the increased risk we observed was due largely to men with serum calcium in the upper portion of the normal reference range (cf. Liefsson and Ahrén). We hypothesize this increased risk may be attributable to factors that control serum calcium levels, such as normal genetic variation in the genes for the calcium-sensing receptor (18).

This study benefits from its prospective design and *a priori* hypothesis. The principal threat to the validity of prospective cohort studies, loss to follow-up for mortality, was low, 3.7%. Our findings could be influenced by bias and confounding. For example, it is possible that that some advanced prostate cancers were undetected at the time of calcium measurement. This would underestimate the positive association between serum calcium and prostate cancer because serum levels of calcium in men with advanced prostate cancer typically are normal or low due to the transfer of calcium from serum into bony lesions (2,19). Second, it is conceivable that some men failed to report advanced prostate cancer that had been treated. The serum calcium levels for such men therefore could reflect the effects of treatment. This possibility is unlikely to have influenced our results because the standard treatment for prostate cancer, androgen-deprivation, does not significantly alter serum levels of calcium or PTH (20). Lastly, it is possible that serum calcium levels are confounded by vitamin D deficiency which is known to elevate serum levels of PTH and may be associated with risk of prostate cancer (21). Vitamin D deficiency is unlikely to be an important confounder in this study because vitamin D deficiency is associated with normal or with low serum calcium (i.e., the opposite of the result observed).

Our results are based on a small number of fatal cases (N = 25) and require confirmation by other prospective studies. If confirmed, these findings have important implications for risk stratification and for prostate cancer prevention. Presently, the only established risk factors for prostate cancer are race and family history. Our finding of a > 2.5- fold increased risk for men in the highest tertile of serum calcium is comparable in magnitude to the increased risk associated with family history (~2.5) and could add significantly to our ability to identify men at increased risk for fatal prostate cancer (22). Most importantly, unlike family history, serum calcium and PTH are factors that can be modified by lifestyle and by pharmacologic means (23).

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Table 1

Selected baseline characteristics of men in the National Epidemiologic Follow-up Study to the first National Health and Nutrition Examination Survey by tertile of serum calcium.

	Serum Calcium		
	Tertile 1	**Tertile 2**	**Tertile 3**
Mean calcium (mg/dl) ± SD	9.3 ± 0.3	9.7 ± 0.1	10.2 ± 0.3
Number of participants	992	807	1012
Age (years)	52.2	48.3	45.5
Body mass index (kg/m^2)	25.9	25.8	25.7
Race (% Black)	11.6	9.7	15.4
Family history of prostate cancer (%)	0.9	1.3	1.3

Table 2

Relative hazards* for incident and fatal prostate cancer by tertile of serum calcium in the National Health and Nutrition Examination Survey's Epidemiologic Follow-up Study.

	Tertile of serum calcium (Median value)			
	Tertile 1 (9.3 mg/dl)	**Tertile 2 (9.7 mg/dl)**	**Tertile 3 (10.1 mg/dl)**	**P-trend**
Prostate cancer incidence				
Number of incident cases	34	22	29	
Person-years at risk	15556	13712	16920	
Age-adjusted Relative Hazards	1.00 (Reference)	0.93 (0.54-1.60)	1.25 (0.76-2.07)	0.409
+BMI	1.00 (Reference)	0.93 (0.54-1.60)	1.25 (0.76-2.07)	0.404
+Race	1.00 (Reference)	0.93 (0.54-1.59)	1.29 (0.78-2.13)	0.361
+Family history	1.00 (Reference)	0.97 (0.56-1.70)	1.31 (0.77-2.20)	0.341
Prostate cancer mortality				
Number of fatal cases	7	7	11	
Person-years at risk	15556	13712	16920	
Age-adjusted Relative Hazards	1.00 (Reference)	1.64 (0.57-4.71)	2.59 (1.00-6.72)	0.049
+BMI	1.00 (Reference)	1.66 (0.58-4.74)	2.62 (1.01-6.80)	0.046
+Race	1.00 (Reference)	1.65 (0.58-4.72)	2.68 (1.02-6.99)	0.043
+Family history	1.00 (Reference)	1.72 (0.55-5.37)	2.68 (0.94-7.64)	0.063

*Each model is adjusted for the listed variable and all prior variables.