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The Relation of Serum Parathyroid Hormone and Serum Calcium to Serum Levels of Prostate-Specific Antigen: A Population-Based Study

Halcyon G. Skinner[1] and **Gary G. Schwartz**[2,3]

[1] University of Wisconsin, Department of Population Health Sciences

[2] Wake Forest University, Departments of Cancer Biology and Epidemiology and Prevention

Abstract

Experimental and clinical data implicate calcium and parathyroid hormone (PTH) in the development of prostate cancer. However, epidemiologic data on the role of these variables in prostate health are sparse. We examined the relationship between serum levels of calcium, PTH and Prostate-Specific Antigen (PSA), an established marker of prostate growth, in a large, population-based study using multivariate linear regression. We studied 895 men in NHANES 2005–2006 who were ≥ 40 years of age and who were without clinical prostate cancer. Adjusted for age, race, BMI and serum levels of 25-Hydroxyvitamin D, serum levels of PTH were significantly positively correlated with serum PSA (P = 0.01). Serum levels of PTH and calcium each were correlated significantly with free PSA (P = 0 .05 and 0 .008, respectively). The percentage of men who had elevated serum levels of PTH (PTH ≥ 66 pg/mL) was significantly greater among African American men (19.2 vs. 9.6%. , P = 0.04). Compared to men whose PTH was at the lower end of the reference range, the predicted PSA for men with a PTH of 66 pg/mL was increased 43%. These findings support the hypothesis that serum calcium and serum PTH stimulate prostate growth in men without clinical prostate cancer and have implications for the use of PSA as a screening tool for prostate cancer.

Keywords

Prostate; Prostate-specific antigen; parathyroid hormone; calcium; vitamin D; NHANES

Introduction

A preventive role for vitamin D in the natural history of prostate cancer was first proposed by Schwartz and Hulka in 1990 (1). Specific receptors (VDR) for the vitamin D hormone, 1,25-Dihydroxyvitamin D, were identified in human prostate cancer cells two years later (2). Demonstrations of anti-proliferative effects of 1,25-Dihydroxyvitamin D on human prostate cancer cells followed quickly thereafter and were followed by demonstrations of other anti-cancer effects, including the inhibition of invasiveness and metastasis (3,4,5,6). The discovery in 1998 that normal prostate cells convert the vitamin D prohormone, 25-Hydroxyvitamin D (25-OHD), into the vitamin D hormone established 1,25-Dihydroxyvitamin D as an autocrine hormone in the prostate (7). In recent years the subject of vitamin D and prostate cancer has burgeoned into a broad scientific field that includes studies of analytic epidemiology, molecular mechanisms and therapeutic and preventive trials (8,9,10,11,12).

[3]Correspondence to: Gary G. Schwartz, Comprehensive Cancer Center of Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157, Ph: 336-716-7446 FAX: 336-716-5687, gschwart@wfubmc.edu.

Although prostate cancer risk has been examined in relation to metabolites of vitamin D in serum and vitamin D-related genes (e.g., Reference 8), other "classical" components of the vitamin D-endocrine system, such as serum calcium and serum parathyroid hormone (PTH), have received comparatively little study. Calcium and PTH are important not only because they regulate serum levels of $1,25(OH)_2D$ and thus may affect prostate cells indirectly, but also because normal and cancerous prostate cells possess specific receptors for calcium and for PTH. Thus, serum calcium and serum PTH may affect prostate cells directly. For example, physiologic levels of both PTH and calcium have been shown to promote the growth of prostate cancer cells in tissue culture and *in vivo* (13,14).

Epidemiologic studies of serum calcium and serum PTH in prostate health are sparse. Two recent studies have shown significant positive associations between high serum calcium and risk of subsequent prostate cancer mortality (15,16) However, to our knowledge, no epidemiologic study has evaluated serum values of calcium and of PTH and prostate growth in men without prostate cancer. In this paper, we examined the cross-sectional relationship of serum calcium, PTH and Prostate-specific Antigen (PSA), an established measure of prostate growth, in a large population-based sample of men, while controlling for covariates including race, BMI, and serum levels of 25-OHD.

Methods

Data were derived from the 2005 – 2006 round of the National Health and Nutrition Examination Survey (2005 – 2006) (17), Three thousand three hundred twenty six (3,326) men participated in NHANES 2006 – 06. We included men who had both a Prostate-specific antigen (PSA) test and had measures of serum calcium and of PTH (n = 895). PSA measurements were made on men aged 40 years and older, excluding those who reported any of the following conditions: current infection or inflammation of the prostate gland, rectal exam in the past week, prostate biopsy in the past month, cystoscopy in the past month, and a history of prostate cancer. We excluded men who had a previously diagnosed cancer, except non-melanoma skin cancer (n=90). Because serum levels of PTH are known to be elevated in chronic kidney disease, we excluded men who reported kidney disease (n=45) including men who reported dialysis within the past year (n=9).

The laboratory procedures used in this study are given in detail in the NHANES Laboratory/ Medical Technologists Procedures Manual and are available via the Internet [4]. Briefly, intact PTH (iPTH) was measured using an Elecsys1010 autoanalyzer (Roche Diagnostics, Mannheim, Germany). The autoanalyzer detects a "sandwich complex" composed of a biotinylated monoclonal PTH-specific antibody and a labeled monoclonal PTH-specific antibody. Coefficients of variability for serum iPTH in this assay are reported as < 10% (18). Total and free PSA were measured using the Access Hybridtech two-site immunoenzymatic "sandwich" assay (Beckman Coulter, Fullerton, CA). Immunodetectable isoforms of PSA in serum include "free" PSA, i.e., PSA that is unbound to protease inhibitors, and "complexed" PSA, i.e., PSA bound to α_1-antichymotrypsin. The principal use of "free PSA" or % free PSA (free PSA/total PSA) is to improve the specificity of PSA in men whose serum total PSA is intermediate (i.e., between 2 and 10 ng.ml), as levels of free PSA above 25% suggest benign prostatic hyperplasia (19).

We evaluated associations between PSA and total serum calcium, serum intact PTH, and serum 25-hydroxyvitamin D. We transformed the PSA variables, intact PTH and calcium using a natural logarithm. We computed associations adjusted for potential confounders using multiple linear regression, including age (in one-year increments), race (black/white), and body mass

[4]Internet address for laboratory methods: http://www.cdc.gov/nchs/nhanes/nhanes2005-2006/lab_methods_05_06.htm

index (BMI; as a continuous measure). Statistical analysis employed SAS (v9.2 for Linux) for data management and R (v2.8.2) with the "Survey Package" (20,21) to account for the complex sampling design of the study and sample weights. All statistical tests were two-sided.

Results

We identified 895 eligible men from the 2005 – 06 round of the National Health and Nutrition Examination Survey. The average age of the population was 55.7 years and 10.5 percent were African American. The average total PSA was 1.48 ng/mL (95% C.I. 1.36 – 1.60) with an average free PSA of 0.38 ng/mL (95% C.I. 0.36 – 0.40). The population Pearson's correlation coefficients of the independent variables were 0.08 for calcium and parathyroid hormone, 0.05 for parathyroid hormone and 25-hydroxyvitamin D, and 0.02 for calcium and 25-hydroxyvitamin D. Characteristics of the study population are shown in Table 1.

Distributions of log transformed total and free PSA were approximately normal, as were distributions of log transformed serum PTH and calcium. Weighted scatter plots of total prostate-specific antigen versus serum total calcium and intact parathyroid hormone indicated no association between total PSA and calcium, but a positive association between total PSA and PTH.

In multivariable adjusted linear regression models, we found that higher concentrations of PTH were associated with higher total and free PSA concentrations. An increase in one standard deviation of log transformed PTH was associated with an increase of 0.9 log units of total PSA ($p < 0.01$) and 0.9log units of free PSA ($p <0.01$). Similarly, we found that serum calcium was significantly associated with free PSA, but not total PSA, adjusting for age, race, body mass index, and serum 25-hydroxyvitamin D concentration. An increase in one standard deviation of log transformed calcium was associated with an increase of 0.05 log units of free PSA ($p < 0.05$).

Discussion

In this population-based sample of men without clinical prostate cancer, we observed significant positive correlations between serum PTH and serum PSA, both total and free, and between serum calcium and free PSA in serum. Serum calcium and serum PTH have been implicated in the pathophysiology of prostate cancer in laboratory and in clinical studies (22, 23). To our knowledge, this is the first study to demonstrate an association between serum PTH and serum calcium and serum PSA in men without clinical prostate cancer.

There are several possible explanations for the positive correlation between serum PTH and serum PSA: chance; serum PSA causes an increase in serum PTH; serum PTH causes an increase in serum PSA, or serum levels of PSA and PTH both are increased by a third factor. Because the sample size is large ($N = 895$, $P = 0.01$) and because a relationship between PTH and PSA was predicted *a priori*, chance is an unlikely explanation (24).

To our knowledge, an increase in serum PTH caused by serum PSA has not been reported. However, it is conceivable that serum PSA could cause a spurious change in serum PTH. PSA cleaves parathyroid hormone related peptide (PTHrP) into fragments (25). PTH and PTHrP share homologies at the amino terminal portion of the molecule. If PSA similarly cleaved PTH, the increased number of PTH fragments could be "read" by a PTH assay as more PTH yielding a false correlation between these analytes. However, the assay for intact PTH is a sandwich assay that requires the presence of two portions of the PTH molecule (17). Thus, if PSA cleaved serum PTH, this conceivably could cause a decrease in the positive correlation between these analytes (i.e., a bias in the opposite direction of the observed correlation).

Alternately, we hypothesize that serum PTH acts to stimulate normal prostate growth which is reflected by an increase in total and in free PSA in serum. Higher values of free PSA in serum are considered evidence of benign growth (26). A role for PTH as a mitogen in the prostate is supported by numerous observations. For example, both normal and cancerous prostate cells express the PTH-1 Receptor, the common receptor for PTH and for parathyroid hormone-related protein. At physiological levels, administration of PTH increases the proliferation of human prostate cancer cells in tissue culture (13). Moreover, the administration of PTH to rats with prostate cancer xenografts promotes tumor growth and is accompanied by an increase in serum PSA (27). Finally, in men with advanced prostate cancer, serum levels of PTH predicted prostate cancer mortality adjusted for the extent of disease (20).

Levels of calcium in serum were significantly correlated with serum levels of free PSA. It is unlikely that serum PSA acts to increase serum calcium, whose serum levels are under strict homeostatic control (28). Specifically, if serum levels of PSA increased serum levels of calcium, then men with advanced prostate cancer would develop hypercalcemia. However, the prevalence of hypercalcemia in prostate cancer is very low, approximately 2% (29). Rather, we hypothesize that calcium levels in serum promote growth in normal prostate cells, akin to the known effects of calcium on cancerous prostate cells. A role for calcium in prostate cancer is supported by several observations. For example, several epidemiologic studies have shown an increased risk for advanced or for fatal prostate cancer among men whose diets are unusually high in calcium(30). Similarly, two prospective studies in men without clinical prostate cancer have shown that high levels of calcium in serum were associated with a significantly increased risk of fatal prostate cancer (15,16). Both normal and cancerous prostate cells posses the calcium-sensing receptor, a G-protein coupled receptor that is activated by extracellular calcium (31). Prostate cells also express calcium-dependent channels that regulate cell proliferation via the control of calcium entry into the cells (32).

Lastly, it is possible that the correlation between serum PSA and serum PTH could be caused by a third factor. For example, prostate cancers that metastasize to bone can cause an increase in both PSA and PTH, as calcium ions are transferred from serum into bony lesions. This causes hypocalcemia and a homeostatic increase in serum PTH (33). However, this relationship could not explain a positive correlation between PSA and PTH in men without bony metastases from prostate cancer. Moreover, this scenario would require a negative correlation between serum calcium and serum PSA, i.e., the opposite of what was observed. Considered together, we believe that our findings are explained most simply by the hypothesis that calcium and PTH are mitogens for prostate cells, whether the cells are cancerous or normal.

Our findings indicate that, like age, race, and BMI, PTH also is associated with total serum PSA (34,35,36). Importantly, many men > 40 years of age had a PTH ≥ 66 pg/mL, the high end of the normal reference range. Compared to men with a PTH at the low end of the reference range (10pg/mL), men with a PTH of 66 pg/mL had a 43% greater PSA. Although the clinical implications of this finding are complex, high levels of PTH could have important consequences for prostate cancer screening. For example, most studies show that PTH levels are significantly and substantially higher among African Americans than among Caucasians, even after adjusting for renal function (37). The proportion of men in our study with a PTH ≥ 66 was twice as high among African Americans(19.2 vs. 9.6, P= 0.04). Similar findings were reported in NHANES 2004–2004 (18). PSA levels among African American men without prostate cancer also are significantly higher than among Caucasians. Consequently, many older African American men without prostate cancer may have a serum PSA that if raised by 43%, could result in a prostate biopsy. This is especially so if the value of PSA that is used as a guide to trigger prostate biopsy is 2.5 ng/mL, as is advocated by many urologists (38).

The prevalence of indolent prostate cancer among older men is high. For example, in the placebo arm of the Prostate Cancer Prevention Trial, men 55 years of age and older who had no prostate symptoms received a prostate biopsy. Twenty two percent (22%) of these men had a positive biopsy(39). Most PSA-detected prostate cancers have a low risk for progression and do not require treatment(40). However, data from the U.S. SEER registry indicate that within 12 months of receiving a positive prostate biopsy, the majority of men with low-risk prostate cancer elected treatment(41). Thus, factors like high serum PTH that are not specific for prostate cancer but which increase the rate of prostate biopsy could contribute to the over-diagnosis and over-treatment of prostate cancer.

This study benefits from the use of a nationally-representative population, uniform laboratory methods, and *a priori* hypotheses. Our study has several limitations. The major limitation is the cross-sectional design which makes the direction of causality for the correlations between serum PTH and serum calcium and PSA uncertain. However, there is sufficient biological knowledge about prostate biology and about mineral homeostasis to exclude, at least provisionally, several alternative explanations. However, because of the study's cross-sectional design, the status of PTH and calcium as stimulators of prostate growth in normal prostate cells should be considered an hypothesis. The ability to maintain normal (i.e., non-transformed) prostate cells in culture may provide an opportunity to examine these hypotheses directly (42).

Other potential limitations of this study include potential confounding by occult chronic kidney disease and by occult prostate cancer. The total immunodetectable PSA in blood is the sum of complexed and free PSA (43). PSA complexed to α_1-antichymotrypsin is the predominant form of PSA in blood *in vivo*. Free, uncomplexed-PSA is a minor fraction, accounting for < 30% of the total PSA in blood (44). Complexed PSA is mainly metabolized in the liver whereas free PSA is removed from the blood by glomerular filtration (45,46). Thus, the quantity of free PSA in blood could be increased by renal dysfunction. Bruun et al. recently reported that the median free PSA in serum was significantly higher in 101 men with moderate to severe chronic kidney disease (median glomerular filtration rate [GFR] of 23 mL/min/1.73 m^2) than among 5264 men attending a prostate cancer screening program who had no evidence of prostate cancer (47). This suggests that moderate to severe chronic kidney disease, which is associated with high serum PTH, potentially could confound a relationship between serum PTH and free PSA. However, chronic kidney disease is unlikely to be an important confounder in this study because men who reported chronic kidney disease were excluded. Moreover, a large survey showed that only 0.3% of normal persons in the U.S. have a GFR less than 30 ml/min/1.73 m^2 and only about 4% have a GFR of 30–60 ml/min/1.73 m^2 (48). Thus, even if some men with unreported chronic kidney disease remained in the data set, their inclusion is unlikely to have materially influenced our findings.

Although men with self-reported prostate cancer also were excluded, it is possible that some men had occult early stage prostate cancer. This is unlikely to have influenced our findings because, unlike fatal cancer, most incident or early stage prostate cancers do not appear to be associated with elevations in serum calcium or PTH (49). Finally, it is possible that our use of the variable total serum calcium may have introduced some information bias. Approximately 45% of total serum calcium is bound to serum proteins, principally albumin. Only the ionized fraction of total serum calcium, which comprises about 50% of total serum calcium, is biologically active. Because PTH decreases the binding of albumin to protein, men with high PTH may have an elevated ionized calcium but a falsely normal total serum calcium (50). Ionized calcium was not measured in NHANES 2005 – 06. The result of the misclassification caused by the use of total serum calcium would be to reduce the observed correlation between total serum calcium and serum PSA.

In conclusion, in this population-based study of men ≥40 years of age who were without clinical prostate cancer, serum levels of PTH were positively correlated with serum levels of PSA, adjusting for the effects of serum vitamin D and other covariates. Serum calcium was significantly correlated with free PSA. If confirmed by other population-based studies, these findings have important implications for the use of PSA as a screening tool for prostate cancer. Men without prostate cancer who have high levels of serum PTH, especially older African American men, may be more likely to receive prostate biopsy than are men with lower levels of serum PTH. This higher rate of biopsy could lead to the increased detection of clinically insignificant prostate cancer (over detection) and to a higher rate of unnecessary treatment.

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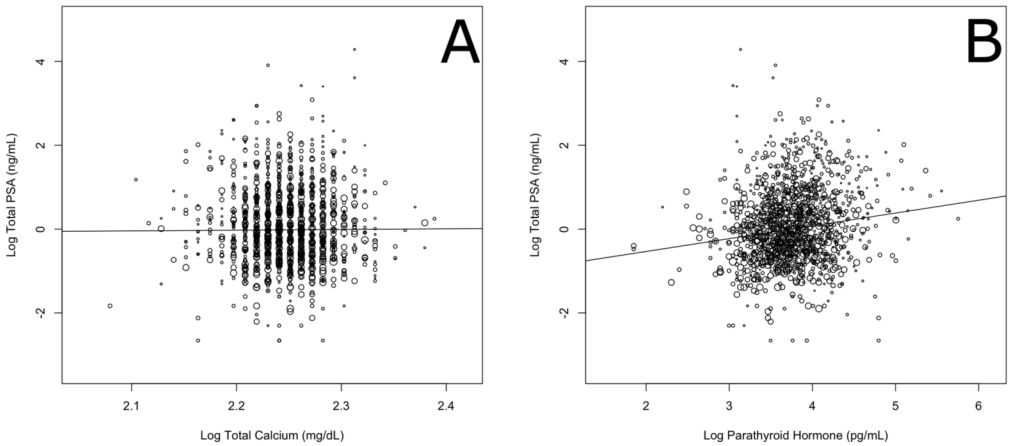

Figure 1.

Weighted plots of serum Prostate-specific antigen (log transformed) versus total serum calcium (Panel A; log transformed) and serum intact parathyroid hormone (Panel B; log transformed) from the 2005 – 06 National Health and Nutrition Examination Survey. The radius of each circle is proportional to the sampling weight of the observation. The lines are unadjusted regressions of serum Prostate-specific antigen on the independent variables. Two observations with extreme calcium values (7.4 and 12.5 mg/dL) do not appear in Panel A, but are included in all statistical analyses.

Table 1

Selected characteristics of men in the 2005 – 06 National Health and Nutrition Examination Survey. Men 40 years and older.

Characteristic	Mean / %	SD
Age (years)	55.7	11.69
African-American (%)	10.5	9.4
Total PSA (ng/mL)	1.48	2.25
Free PSA (ng/mL)	0.38	0.39
Total Calcium (mg/dL)	9.48	0.34
Intact Parathyroid Hormone (pg/mL)	45.1	21.76
25-hydroxyvitamin D (ng/dL)	21.7	7.73
Body Mass Index (kg/m^2)	29.1	6.07

Estimates and standard deviations account for the complex sampling design of NHANES.

Table 2

Linear regression results of total and free prostate specific antigen (PSA) concentrations (log transformed) versus total serum calcium (log transformed) and intact parathyroid hormone concentrations (log transformed) among United States men aged 40 years and greater in the National Health and Nutrition Examination Survey (2005 – 06).

Free PSA (log ng/mL)	**Estimate**	**Standard Error**	**P-value**
Log Calcium (per SD mg/dl)	0.046	0.020	0.05
Log Parathyroid Hormone (per SD pg/mL)	0.089	0.026	0.01
25-Hydroxyvitamin D (per SD ng/dL)	0.045	0.024	0.09
Body Mass Index (per SD kg/m^2)	−0.100	0.013	<0.01
Age (years)	0.024	0.003	<0.01
Black race (yes/no)	0.103	0.064	0.14
Total PSA (log ng/mL)			
Log Calcium (per SD mg/dl)	0.035	0.031	0.29
Log Parathyroid Hormone (per SD pg/mL)	0.086	0.027	0.01
25-Hydroxyvitamin D (per SD ng/dL)	0.024	0.003	0.37
Body Mass Index (per SD kg/m^2)	−0.084	0.013	<0.01
Age (years)	0.027	0.002	<0.01
Black race (yes/no)	0.126	0.064	0.08

Models account for the complex sampling design of NHANES. The dependent variables total and free PSA were log transformed. The independent variables total calcium and intact parathyroid hormone were log transformed. SD stands for standard deviation. Each of the independent variables, log calcium, log parathyroid hormone, 25-hydroxyvitamin D, and body mass index, were scaled to units of one standard deviation of their respective distributions.