

Rise in Prostate-Specific Antigen in Men With Untreated Low-Grade Prostate Cancer Is Slower During Spring-Summer

R. Vieth,* R. Choo, L. Deboer, C. Danjoux, G.C. Morton, and G. Klotz

To test the hypothesis that the rate of rise in prostate-specific antigen (PSA) is slower during the spring-summer than during the rest of the year, we used PSA data from a prospective single-arm cohort study of men who had been followed to characterize a watchful observation protocol with selective delayed intervention for clinically localized, low-to-intermediate grade prostate adenocarcinoma. The rate of PSA increase was calculated as the visit-to-visit slope of log(PSA) against time, from 1 calendar-quarter visit to the next. The nonparametric Friedman test confirmed differences in rate of PSA rise among the calendar quarters ($P = 0.041$). Post hoc analysis showed the rate of PSA increase during Q2 was significantly slower than in each one of the other calendar quarters (Q1 versus Q2, $P = 0.025$; Q3 versus Q2, $P = 0.002$; Q4 versus Q2, $P = 0.013$), with no differences among quarters Q1, Q3, and Q4. These results are consistent with the vitamin D hypothesis that the higher 25-hydroxyvitamin D levels associated with spring and summer have a desirable effect on prostate biology. The therapeutic implication is that vitamin D supplementation in the range of 2000 IU/d, a dose comparable to the effect of summer, can benefit men monitored for rising PSA.

Keywords: seasonal, sunshine, ultraviolet light, cholecalciferol, enzyme kinetics, calcidiol, calcitriol, prostate cancer, prevention

INTRODUCTION

Season of the year affects vitamin D nutritional status. Summer sunshine contains the UVB radiation (285–300 nm) that disrupts dermal 7-dehydrocholesterol, and this then isomerizes into vitamin D₃.¹ The liver readily hydroxylates vitamin D₃ at carbon 25, producing 25-hydroxyvitamin D (calcidiol). In populations living in temperate latitudes, calcidiol levels rise and fall in annual cycles.²

In the traditional sense, calcidiol is the substrate used by renal tissue to produce the calcium-regulating

hormone calcitriol. However, many tissues, including prostate, possess calcidiol-1-hydroxylase, which converts circulating calcidiol into calcitriol. In nonrenal tissues, calcitriol is a paracrine molecule that promotes cellular differentiation and reduces proliferation.³ The capacity of prostate cells to generate calcitriol is directly proportional to the supply of its precursor, calcidiol.^{3–6} There is a growing school of thought that vitamin D nutrition has desirable effects on prostate cells.

In Nordic countries, mortality from prostate and several other cancers is lower if they are diagnosed during the summer than during the winter. This seasonal effect was attributed to desirable biologic effects of higher summertime vitamin D status.⁷ However, both low and high extremes of calcidiol concentrations are associated with higher risk of prostate cancer in Nordic countries.⁸ To explain this paradox, we have proposed that the parts of the year when calcidiol concentrations are in decline are associated with suboptimal concentrations of calcitriol in prostate tissue.⁹ We

Mount Sinai Hospital, Toronto-Sunnybrook Regional Cancer Center, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Toronto, Canada.

*Address for correspondence: Pathology and Laboratory Medicine, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario, Canada M5G 1X5. E-mail: rvieth@mtsinai.on.ca

proposed that not only are low calcidiol levels themselves detrimental to the prostate, but so are dynamically falling calcidiol levels. The present analysis of data was done to test the hypothesis that season affects prostate biology in a manner consistent with a refinement of the vitamin D hypothesis, ie, that both low and dynamically falling calcidiol levels have undesirable effects in the context of cancer.

In men without prostate cancer, most prostate-specific antigen (PSA) is derived from the normal glandular epithelial cells of the transition zone, often as the consequence of benign, age-related, prostatic hyperplasia (hypertrophy). Serum PSA levels reflect the number of PSA-producing cells, the inherent synthesis rate of PSA, and the rate of diffusion into the blood circulation. The rate of rise in PSA is thought to offer insight to underlying tumor kinetics. In conjunction with traditional clinical and histologic variables, this may help in the management of patients based on the biologic behavior of the malignancy. The rate of rise in PSA has been proposed as a useful endpoint in prevention research,¹⁰ and knowledge of the rate of rise of PSA is increasingly being incorporated into clinical decision making for patients with prostate cancer.¹⁰⁻¹⁴ An understanding of how season affects PSA could be an important component of the assessment of the significance of PSA rise in a given patient.

We have reported a preliminary study of the vitamin D hypothesis, and found that 2000 IU/d of vitamin D supplement slowed the rate of rise in PSA in men who were biochemical failures (because of rising PSA) following radical prostatectomy or radiation for prostate cancer.¹⁵ As a further test of the vitamin D hypothesis, we now report on our analysis of longitudinal PSA data from a previously published cohort of men to determine whether the rate of rise in PSA varies with season.¹²

METHOD

The data are from a prospective, single-arm cohort study in progress since November 1995 to characterize a watchful observation protocol with selective delayed intervention for clinically localized, low-to-intermediate grade prostate adenocarcinoma.¹² Men were observed with selective delayed intervention using clinical, histologic and/or PSA progression as a treatment indication. The study had been approved by the Research Ethics Committee of Sunnybrook and Women's Hospital, Toronto. Each subject was conservatively managed with watchful observation alone as long as he did not meet the criteria of disease progression. Disease progression was empirically defined based on three criteria: the rate

of PSA increase, clinical progression, and histologic upgrading on repeat prostate biopsy. When a patient met any of these predefined criteria during the follow-up, he was taken off the watchful observation policy and appropriate treatment was implemented according to his age, extent of disease, and comorbidity. Patients were closely monitored to maximize the likelihood of intervening within the therapeutic window of curability. Each patient was screened according to defined inclusion and exclusion criteria, and enrolled into the study if all the following eligibility criteria were met:

- (i) histologic diagnosis of adenocarcinoma of prostate within 12 months before entry
- (ii) no previous treatment of prostate carcinoma
- (iii) clinical stage T1b-T2b N0M0 (1997 TNM classification)
- (iv) a PSA level of <15 ng/mL
- (v) a Gleason score of <8
- (vi) patient signed informed consent

Patients were followed every 3 months for the first 2 years and every 6 months thereafter as long as they remained in the study. At each visit, a medical history was obtained, physical examination including a digital rectal examination was performed, and circulating PSA, prostatic alkaline phosphatase, and serum creatinine were measured. Patients had transrectal ultrasound (TRUS) of the prostate every 6 months and TRUS-guided rebiopsy of the prostate at 18 months after enrollment. Bone scans were taken annually for the first 2 years and then biennially as long as the patient remained on surveillance.

Disease progression resulting in therapeutic intervention was empirically defined, and this consisted of 3 categories: clinical, histologic, and PSA progression. The patient was considered to have clinical progression when he developed one of the following:

- (i) more than a doubling of the product of the maximum perpendicular diameters of the primary lesion, as measured digitally
- (ii) symptoms requiring transurethral resection of the prostate (TURP)
- (iii) ureteric obstruction
- (iv) radiologic and/or clinical evidence of distant metastasis

Patients who required TURP were conservatively scored as having progressed, although obstructive urinary symptoms could be caused by progression of either malignancy or coexisting BPH. Furthermore, TURP prevented further PSA monitoring. Histologic progression occurred when the Gleason score was upgraded to ≥ 8 in the prostate rebiopsy at

12–18 months after study enrollment. PSA progression was defined when all of the following 3 conditions were met:

- (i) PSA doubling time <2 years, based on at least 3 separate measurements over at least 6 months
- (ii) a final PSA level of >8 ng/mL
- (iii) $P < 0.05$ from a regression analysis of $\ln(\text{PSA})$ against time, ie, the slope of this plot is statistically significantly different from zero

The study closed in November 2001 after accruing 251 patients; 7 failed to meet the eligibility criteria and were excluded from the study, leaving 244 eligible in the study. As of March 2003, the median (range) follow-up of this cohort was 44 (range, 3–85) months; 145 patients remained on the surveillance protocol with no disease progression at the time of this report, whereas 99 had left the study for various reasons presented previously.¹² Fifty-one patients met the definition of disease progression (23 with clinical, 10 with histologic, and 18 with PSA progression) and subsequently received therapeutic intervention. None of these patients had any evidence of distant metastasis when they were declared to have disease progression.

Of 244 patients initially enrolled, 231 patients had at least 6 months of follow-up and a minimum of 3 PSA measurements, and these were included for the assessment of seasonal variability of the rate of PSA rise. A total of 2395 PSA determinations were used for the analyses reported here. Data for all 4 calendar quarters were available on 192 patients. For each man for whom data were available for more than 1 year, the rate of PSA increase used in our analysis for each calendar quarter was the average of his available rates of increase for that quarter.

The median age of the 231 patients at study enrollment was 71 (range, 49–84) years, and their characteristics according to initial PSA level, Gleason score, and clinical stage are summarized elsewhere.¹² The median (range) initial PSA at enrollment was 6.5 (0.3–14.6) ng/mL. The median follow-up of the cohort was 45 (range, 12–85) months and the median number of PSA measurements was 8 (range, 4–21).¹²

Serum PSA was measured using the Hybritech assay (San Diego, CA). The rate of PSA increase was calculated as the slope of $\log(\text{PSA})$ against time, from one calendar-quarter visit to the next. For example: a slope value for “Q2” is the rate of rise (delta $\log \text{PSA}$ versus delta days) for the PSA measured in the second calendar quarter (April, May, or June), with the next PSA measured in the third calendar quarter, Q3 (July, August, or September). To express the rate of rise in a

more understandable way, we converted the slope of $\log \text{PSA}$ versus days into units of percent change per month:

$$\begin{aligned} \% \text{ rise in PSA/mo} &= 100\% \\ &\times [\text{antilog}(\text{slope of } \log \text{ PSA/d}) \\ &\times (30.42 \text{ days/mo}) - 1] \end{aligned}$$

Statistical analysis

Analyses were carried out using SPSS software, version 12 (Chicago, IL). We used nonparametric tests because the data were not distributed in a Gaussian manner and the data were both positive and negative, complicating the usual “normalization” procedures. The Friedman test was used to determine whether the ranking of repeated samples per subject tended to vary among calendar quarters (Q1–Q4). Post hoc testing between paired values was done using the Wilcoxon rank-sum test. Adjustment for multiple post hoc comparisons was done using Holm’s sequential Bonferroni method for control of type 1 error for all pairwise comparisons.^{16,17}

RESULTS

The quartile values for the rise in PSA for each calendar quarter are presented in Figure 1. The nonparametric Friedman test for repeated samples per subject indicated that the mean rank of rise in at least 1 calendar quarter differed from that of the other calendar quarters ($P = 0.041$, Table 1). Paired comparisons between individual calendar quarters were performed using the Wilcoxon signed rank test (Table 2). These indicated that the rise in PSA during Q2 was significantly lower than in each one of the other calendar quarters, with no significant differences among Q1, Q3, and Q4. After adjustment for post hoc comparisons, assuming none of

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T1
T2

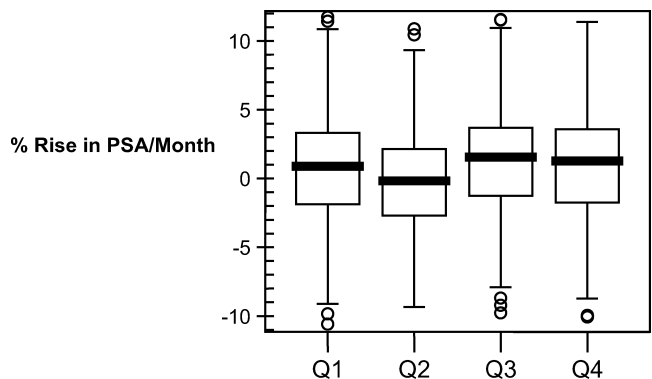


FIGURE 1. Quartile values for rate of rise in PSA in each calendar quarter in men being monitored with low to intermediate grade prostate cancer.

Table 1. Results of the Friedman test, comparing rank of rate of rise in PSA among calendar quarters.

Calendar quarter	Mean rank*	Median % PSA rise/mo
Q1	2.46	0.88
Q2	2.30	-0.17
Q3	2.64	1.54
Q4	2.60	1.27

*N = 192 patients, $\chi^2 = 8.269$, $df = 3$, $P = 0.041$. The mean rank overall is 2.5.

the 6 possible comparisons had been specified beforehand, only the Q2 versus Q3 contrast remained significant based on 2-tail hypothesis testing. After Holm's adjustment, but using the 1-tail differences expected prior to the analysis, the rate of rise in PSA during Q2 remained significantly less than during each other calendar quarter.

F2 Figure 2 shows the cumulation in the percentage increase in value of PSA across 1 year, based on the median quarterly monthly increases in PSA from Table 1. Previously reported calcidiol levels in Toronto show the annual cycle in calcidiol levels. Together, the patterns of seasonal calcidiol and PSA levels suggest that PSA levels rose during the first calendar quarter, when calcidiol levels were at their lowest, and they rose again during the third and fourth calendar quarters when calcidiol levels were in active decline. In contrast, PSA levels tended not to differ between the measurements taken between the second and third quarter of each year, ie, no significant change between spring and summer.

DISCUSSION

The present results are consistent with the vitamin D hypothesis, that higher calcidiol levels associated with

sun exposure during spring and summer have a desirable effect on the biology of the prostate. We base this conclusion on the observed seasonal differences in the behavior of the prostate biomarker, PSA. The slower rate of rise in PSA during the summer may reflect a diminished growth or proliferation rate of PSA-producing cells, a slowdown in replication of cancer cells, or a transient stabilization in synthesis of PSA by normal or neoplastic cells.

In our recent study of men whose PSA was rising despite curative treatment of prostate cancer, the institution of vitamin D supplementation at the safe upper limit (UL) for the general public, 2000 IU/d, resulted in a substantial reduction in the rate of rise in PSA.¹⁵ The cohort of men whom we describe in this study differs because their prostate cancer was of low to moderate grade and the men had not undergone curative treatment. This was effectively a study of Nature's intervention with vitamin D, in which the spring-summer rise in calcidiol is roughly equivalent to the annual institution of 1000–2000 IU/d of vitamin D.¹⁸ Because the resulting rate of rise in PSA was slower only during the rising phase of calcidiol levels, the present study is consistent with both the findings of our earlier vitamin D₃ supplementation study that produced sustained increases in calcidiol¹⁵ and the hypothesis that tissue calcitriol levels are suboptimal during the annual declining phase of calcidiol.⁹

The contrast between the Q2 to the Q3 is particularly interesting. Despite similar average calcidiol levels during these times (Fig. 2), the median rise in PSA was marginally negative during Q2, but distinctly positive during Q3 (Fig. 2). This had been predicted from our previously published hypothesis that actively falling calcidiol concentrations, in addition to low calcidiol concentrations, are detrimental to prostate biology.⁹ In short, paracrine production of calcitriol within prostate tissue is determined by the combined action of substrate calcidiol driving synthesis of calcitriol and

Table 2. Wilcoxon signed rank test and correction for multiple comparisons between pairs of quarterly rate of rise in PSA.

Paired contrast*	Q1-Q2	Q3-Q2	Q4-Q2	Q3-Q1	Q4-Q1	Q4-Q3
Z	-2.24	-3.04	-2.48	-0.58	-0.50	-0.05
Pairwise P (2-tailed)	0.025	0.002	0.013	0.564	0.617	0.963
Holm's corrected P [†]	0.10	0.012	0.06			

*Contrasts compare the rate of increase in PSA between 2 calendar quarters. For example, Q1-Q2 indicates a comparison of slopes, where each Q1 slope is based on the rise in PSA measured in January-March to the next PSA measured in Q2 (April-June); each Q2 slope is based on the rise in PSA measured April-June to the next PSA measured in Q3 (July-September).

[†]Holm's correction of each pairwise P value that was <0.05. This controls for type 1 error for all 6 possible 2-tailed contrasts, and it assumes that the analysis had been intended, solely for post hoc testing of all possible hypotheses¹⁶; however, this increases the probability of failing to accept true differences.

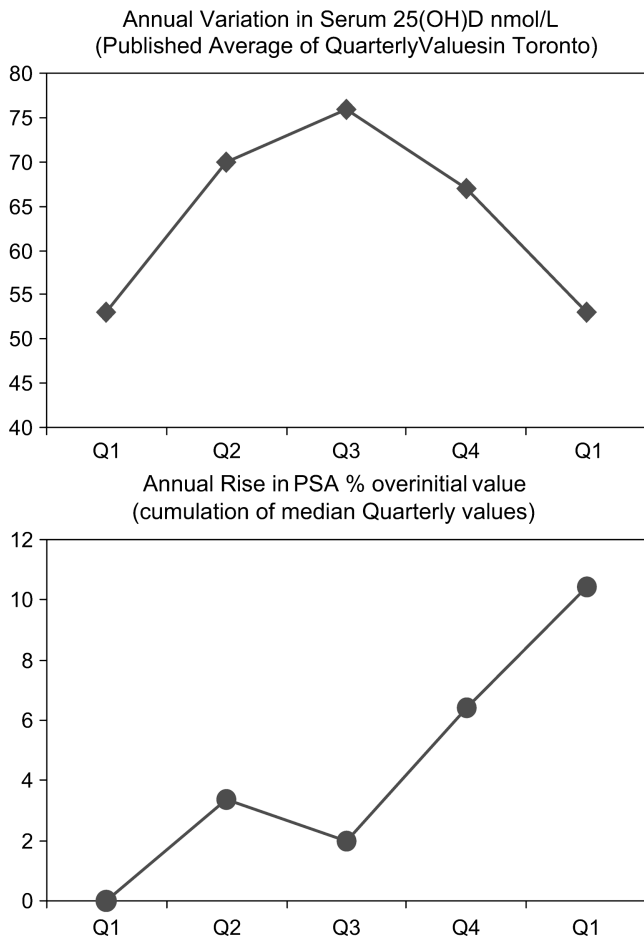


FIGURE 2. Comparison of the annual pattern of calcidiol levels from an earlier study in Toronto women² with the annual progression in PSA based on median values of the present study.

catabolism of calcitriol by 24-hydroxylase.³ The catabolic pathway is poorly regulated, so that whereas calcidiol levels fall, the catabolic enzyme can never quite decline enough to keep tissue calcitriol levels stable. The hypothesis posits that progressively declining calcidiol levels must be compensated for by either higher amounts of tissue 1-hydroxylase or lower tissue 24-hydroxylase. A lag in the adjustment of either enzyme will result in suboptimal tissue concentrations of calcitriol.⁹ More conclusive evidence to support this theory will require experimental studies involving assay of prostate calcitriol content under various conditions of circulating calcidiol.

One problem with the present study is that we did not use the conventional approaches to calculate the rate of rise in PSA, or the doubling time, that involve linear regression of several data points for each patient. The conventional approach to the slope effectively produces an average value that crosses seasons, making

it impossible to detect differences between seasons. We were able to observe seasonal fluctuations in rate by minimizing the time interval for each PSA rate calculation. However, this increased the imprecision of each measure of slope. For the purpose of testing the hypothesis of seasonal differences in rate, individual variability was overcome with a large sample size. For individual patients, seasonal differences in the rate of rise in PSA will be difficult to detect.

There has been growing interest in the rate at which PSA goes up in patients with prostate cancer because this appears to have prognostic value.¹⁰⁻¹⁴ The present findings show that seasonal variation in vitamin D status affects that rate of rise. To date, the clinical research involving the vitamin D system and prostate cancer has focused on administration of calcitriol and its analogues.^{19,20} However, sunshine and vitamin D supplementation raise only calcidiol,^{21,22} which functions by facilitating paracrine production of calcitriol within prostate tissue. The strategy of increasing vitamin D nutrition to 2000 IU/d is remarkably safe,^{23,24} producing calcidiol levels that benefit prostate cancer prevention and treatment.¹⁵ We regard vitamin D as a background, not as a substitute, to other therapy being considered. There is a second major benefit of doing this. Because prostate cancer patients are at higher risk of osteoporosis,²⁵ vitamin D supplementation should be instituted for them and for all older men to target a calcidiol concentration that is higher than 30 ng/mL (75 nmol/L).²⁶

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