

Prostate Cancer, Serum Parathyroid Hormone, and the Progression of Skeletal Metastases

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Abstract

Bony metastases from prostate cancer are a significant cause of morbidity and mortality. These metastases are predominantly blastic (bone-forming) and commonly cause increased serum levels of parathyroid hormone (PTH) as calcium ions are transferred from serum into blastic bone. The epidemiologic and clinical significance of secondary hyperparathyroidism in advanced prostate cancer have not been widely appreciated. Prostate cancer bony metastases show increased expression of the PTH receptor (PTH-IR) and PTH promotes the growth and invasiveness of prostate cancer cells in bone. Thus, blastic

metastases appear to induce a "vicious cycle" in which PTH resorbs normal bone to support the growth of blastic bone. Recognition of the potential role of PTH in the progression of skeletal metastases suggests novel opportunities for prostate cancer secondary prevention. In particular, we propose that suppressing serum PTH in advanced prostate cancer may reduce morbidity by decreasing fractures and pain caused by bone resorption and may reduce mortality by retarding the progression of metastatic disease. (Cancer Epidemiol Biomarkers Prev 2008; 17(3):478–83)

Introduction

Prostate cancer accounts for more than 27,000 deaths in the United States per year (1). At autopsy, bony metastases are found in ~60% to 85% of men with prostate cancer and are a major cause of pain, disability, and death (2). Unlike most cancers that metastasize to bone (e.g., breast and lung), which produce lytic lesions, the bony metastases from prostate cancer are predominantly blastic (bone-forming), although they also contain a lytic component (3). Osteoblastic metastases occur at sites of previous osteoclastic bone resorption and are typified by weak, poorly organized woven bone that predisposes the site to fracture (4).

In 1962, Ludwig observed that metastases from prostate cancer cause increased serum levels of parathyroid hormone (PTH). However, the epidemiologic and clinical implications of that observation have been little appreciated. PTH is now understood to be a mitogen for prostate cancer cells (5). We propose that serum PTH promotes the progression of prostate cancer in bone. A corollary of this hypothesis is that suppressing serum PTH may retard the progression of bony metastases. To place this hypothesis in context, we briefly review the physiology of hyperparathyroidism.

Mechanism of Secondary Hyperparathyroidism in Metastatic Prostate Cancer

The parathyroids are four small glands located on the posterior aspect of the thyroid that function to regulate serum calcium within a narrow range (~8.5-10.0 mg/dL). When calcium levels dip below this threshold, the calcium sensing receptor on parathyroid cells is activated, stimulating parathyroid cells to secrete PTH (6). PTH functions to increase calcium uptake in the gut and to mobilize calcium from bone (7). An adenoma of one or more parathyroid glands produces primary hyperparathyroidism, a condition marked by inappropriately high PTH and high serum calcium. Conversely, secondary hyperparathyroidism occurs when the serum PTH level is elevated adaptively in response to low serum calcium. Secondary hyperparathyroidism is commonly observed in chronic kidney disease in which reduced renal function results in low levels of 1,25(OH)₂D leading to hypocalcemia, stimulating the parathyroids to secrete PTH (8, 9).

In addition to chronic kidney disease, secondary hyperparathyroidism also is observed in the "hungry bone syndrome" found post-parathyroidectomy and post-renal transplantation and in metastatic prostate cancer (10-13). Ludwig succinctly described the pathophysiology of this syndrome in prostate cancer: "The sequence of metabolic events is as follows. (1) Osteoblastic metastases cause an increased deposition of calcium and phosphate in bone, tending to decrease serum concentrations of both ions. (2) Hypocalcemia is thereby induced, and this results in stimulation of the parathyroid glands. (3) Secondary hyperparathyroidism then causes a further decrease in serum phosphate concentration. ... (4) Treatment with estrogens, which are known to enhance deposition of calcium and

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phosphate into bone, provokes the development of hypocalcemia or aggravates it if it is already present" (13).

Secondary Hyperparathyroidism Is Common in Metastatic Prostate Cancer

The pathophysiology described by Ludwig appears to be a common feature of metastatic prostate cancer. There are numerous case reports documenting hypocalcemia and elevated serum PTH in men with prostate cancer (e.g., refs. 14-19). Moreover, case series reported by Berruti et al. (20), Buchs et al. (21), and Murray et al. (22) indicate that the prevalence of secondary hyperparathyroidism in advanced prostate cancer ranges from 21 to 57%.

Berruti et al. studied 90 men with metastatic prostate cancer. All had progressive disease and were off any systemic treatment for at least 1 month and palliative radiotherapy for at least 3 months. Patients with previous or current bisphosphonate treatment were excluded. These patients had a median serum PTH of 32 ng/L [range, 10-190 ng/L; normal range, ~10-65 ng/L (pg/mL)]. Twenty-one percent of the prostate cancer patients had significantly elevated PTH (PTH \geq 65 pg/mL). Similarly, Buchs et al. compared 27 patients with prostate cancer and bone metastases to 12 prostate cancer patients of similar age without bone metastases. The mean PTH in pmol/L (\pm SE) for patients with bone metastases was 6.5 ± 1.0 pmol/L (62 ± 9.5 pg/mL) versus 5.4 ± 0.7 pmol/L (51 ± 6.7 pg/mL) for patients without bone metastases. The upper limit of the normal range for PTH reported by these authors is 6.0 pmol/L (57 pg/mL). Thus, elevated serum levels of PTH were found in more than 50% of patients with bone metastases.

Murray et al. studied 131 men with metastatic (locally advanced and distant) prostate cancer. Compared to a group of 108 male volunteers of similar age without prostate cancer and with normal kidney function, 34% of the prostate cancer patients had significantly elevated serum PTH [PTH \geq 70 pmol/L (67 pg/mL)]. Men with proven bone metastases (determined by bone scan) had significantly higher PTH than prostate cancer patients without proven metastases [7.3 ± 0.5 pmol/L (69 ± 5 pg/mL) versus 4.3 ± 0.4 pmol/L (41 ± 4 pg/mL), respectively; $P < 0.0005$]. Among 65 men with bone metastases and progressive disease (prostate-specific antigen \geq 125% of baseline), the prevalence of elevated serum PTH was 57%. Importantly, in 44% of the prostate cancer patients, the elevated PTH occurred in association with normal serum calcium, a phenomenon known as "normocalcemic hyperparathyroidism" (that is, the serum calcium is within the normal range at the expense of significantly elevated serum PTH; ref. 23).

The occurrence of normocalcemic hyperparathyroidism may explain why the association between prostate cancer and elevated serum PTH has not been widely recognized: because PTH is measured only in response to an abnormal serum calcium, the secondary hyperparathyroidism will not be detected (24). Evidence that the elevated PTH may be causally related to skeletal metastases is provided by the demonstration that the experimental infusion of human PTH to men with prostate cancer increased urinary levels of N-telopeptide (25), a marker of bone resorption that has been correlated prospectively with the progression of bony metastases (26).

Other than prostate cancer metastases, other mechanisms could account for the high prevalence of elevated PTH in men with advanced prostate cancer, including illness-associated vitamin D deficiency and ectopic production of PTH by the prostate tumor. A large body of epidemiologic studies supports the hypothesis, first proposed in 1990 (27), that vitamin D deficiency increases the risk for clinical prostate cancer (28). The major mechanism for the protective effect of vitamin D is believed to be the prostatic conversion of the vitamin D prohormone, 25-hydroxyvitamin D, into the active hormone, 1,25(OH)₂D, which binds to the prostatic receptor for 1,25(OH)₂D (the vitamin D receptor) and exerts prodifferentiating, antiproliferative, and antimetastatic effects on prostatic cells (29). It is possible that an additional mechanism by which vitamin D deficiency increases prostate cancer risk is via stimulation of PTH (30). However, although serum levels of PTH are increased by vitamin D deficiency (e.g., 25-hydroxyvitamin D levels < 20 ng/mL), the magnitude of this effect on PTH is $< 15\%$, which appears inadequate to explain the prevalence and magnitude of the PTH elevations observed in men with advanced prostate cancer (31).

Alternately, an association between elevated PTH and advanced prostate cancer could occur if prostate tumors produced PTH. Ectopic production of PTH by tumors is very rare (32) and, to our knowledge, has not been reported for prostate tumors. However, this possibility is an unlikely explanation because ectopic production of PTH would be expected to cause hypercalcemia, which is seldom observed in prostate cancer (see below).

PTH Promotes the Proliferation and Migration of Prostate Cancer Cells and Negatively Predicts Survival

In addition to its "classic" role in regulating serum calcium, PTH promotes the proliferation and migration of prostate cancer cells *in vitro* and *in vivo*. *In vitro*, PTH increases the proliferation of LNCaP and DU-145 human prostate cancer cells and increases chemotaxis in LNCaP, DU-145, and PC-3 cells (5). *In vivo*, the incidence of skeletal metastatic foci was significantly increased in mice treated with PTH versus mice treated with saline (33). At least part of the mechanism underlying these effects is the expression on prostate cancer cells of the common receptor for PTH and PTH-related protein, the PTH type I receptor (PTH-IR).

PTH-related protein is an autocrine growth factor made by prostate and other cancer cells, which aids in their progression in bone (34-36). PTH-related protein was originally identified as the peptide responsible for humoral hypercalcemia of malignancy. An extensive review of the literature indicates that hypercalcemia is exceptionally rare in prostate cancer, occurring in $< 2\%$ of cases (37, 38). PTH and PTH-related protein are immunologically distinct proteins that bind with equal affinity to the PTH-IR, which is highly expressed on prostate cancer bony metastases (39). Using immunohistochemistry and *in situ* hybridization, Iddon et al. found significantly higher expression of the PTH-IR in pathologic samples from human bony metastases from prostate cancer than in the primary tumors (86% versus 19%, respectively; ref. 40). Similar findings were reported

by Pérez-Martínez et al. who reported significantly higher PTH-IR expression in high-grade versus low-grade prostate cancers (41). This suggests that an increased sensitivity of prostate cancers to PTH also may contribute to the progression of metastases in bone.

We conducted a phase I/II clinical trial to evaluate a 1,25-dihydroxyvitamin D analogue in 18 men with advanced androgen-insensitive prostate cancer. No men had prior treatment with bisphosphonates. In that trial, serum levels of PTH before treatment were significantly and negatively associated with survival; the higher the serum PTH, the shorter the survival ($P < 0.01$). The survival curve as a function of baseline PTH is shown in Fig. 1. For every 25 pg/mL increase in serum PTH, the hazard of dying increased by 22% (95% confidence interval for hazard ratio, 1.03-1.43; $P = 0.01$, by log-rank test). The estimated median survivals for baseline PTH of 3, 70, and 400 pg/mL (which represent the minimum, median, and maximum baseline values) were 21.2, 10.7, and 4.0 months, respectively (42). We used serum prostate-specific antigen as a marker of extent of disease and used a Cox regression model that included both prostate-specific antigen and PTH in the model. The relationship between survival and initial prostate-specific antigen was not significant ($P = 0.97$), but the effect of PTH remained significant ($P = 0.02$). This indicates that the survival effect associated with PTH persisted after adjustment for disease severity. Because serum levels of creatinine and 25-OHD were normal in the majority of these men, these results were not the result of renal insufficiency or vitamin D deficiency.

The PTH-Prostate Cancer Progression Hypothesis

In summary, the observations that

1. elevated serum PTH is common in men with bony metastases from prostate cancer,
2. prostate cancer bony metastases show high expression of the PTH receptor,

3. PTH promotes the proliferation and metastasis of prostate cancer cells *in vitro* and *in vivo*, and
4. elevated serum PTH in men with prostate cancer is associated with increased mortality.

support the hypothesis that serum PTH promotes the progression of prostate cancer in bone (see Fig. 2).

The PTH-prostate cancer progression hypothesis makes novel predictions and may illuminate several epidemiologic findings that are presently unexplained. For example, prostate cancer mortality should be elevated among men with both primary and secondary hyperparathyroidism. We were unable to locate data that specifically address the question of primary hyperparathyroidism. However, in a Swedish population-based registry of persons hospitalized for parathyroid disease, Nilsson et al. reported a significant increase in male deaths from tumor (standardized mortality ratio, 1.31; 95% confidence interval, 1.03-1.61; *International Classification of Diseases, Tenth Edition* codes C00-D48), a category that would be expected to include a high proportion of deaths from prostate cancer (43).

It has been observed repeatedly that, even after matching for stage of disease, African Americans with prostate cancer have a poorer survival than Caucasians (44-46). Our hypothesis is consistent with these observations as it is well known that African Americans have higher serum levels of PTH than Caucasians even after controlling for renal function (47). For example, in 260 Caucasians and 103 African Americans with secondary hyperparathyroidism (due to chronic kidney disease), serum PTH levels were 383 ± 33 pg/mL in the African Americans versus 246 ± 19 pg/mL in the Caucasians despite similar serum levels of calcium, phosphorus, and alkaline phosphatase in the two groups (48).

An important corollary of this hypothesis is that suppression of PTH may retard the progression of bony metastases. We propose that, in addition to suppressing

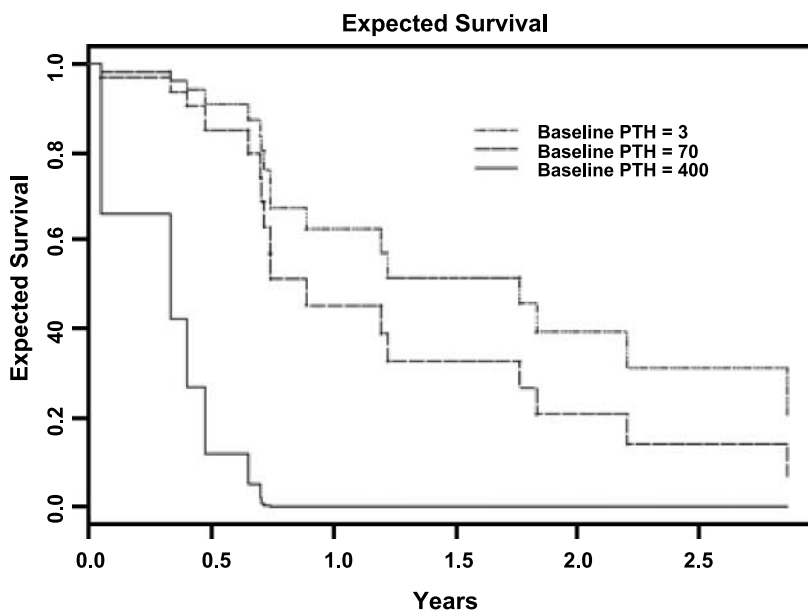


Figure 1. Kaplan-Meier plot of survival for 17 patients as a function of initial PTH. These data show a significant inverse relationship between serum PTH and prostate cancer survival (from ref. 42).

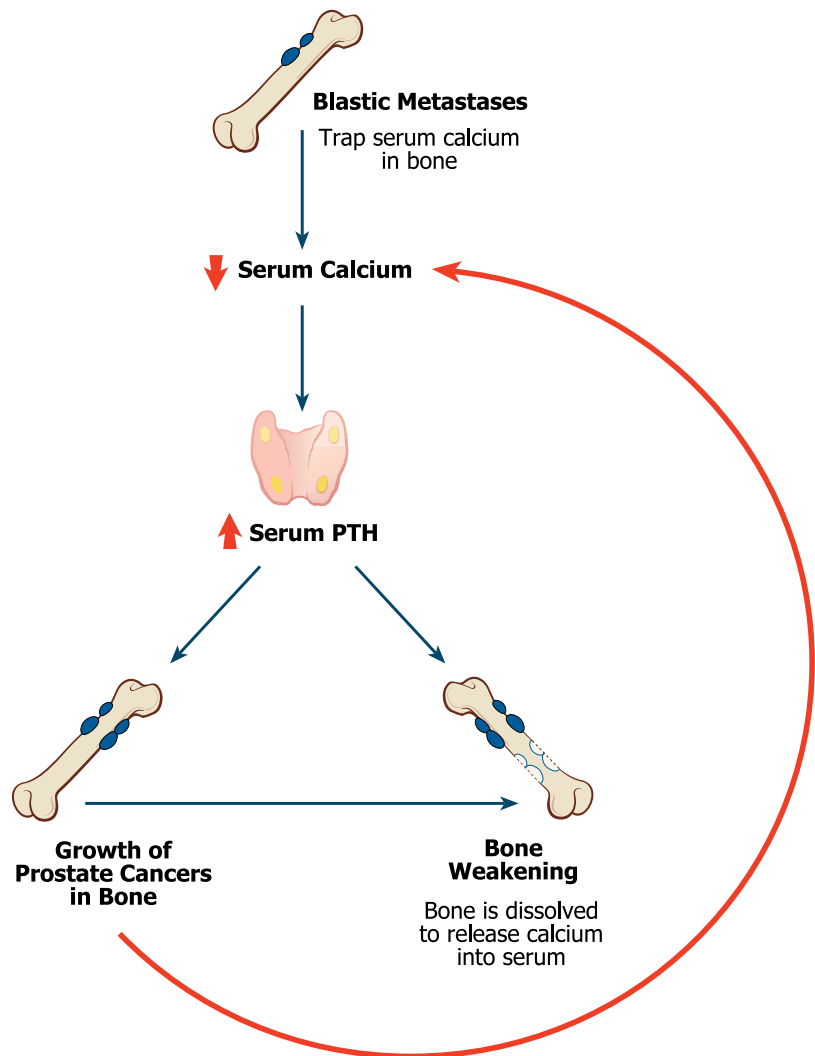


Figure 2. The PTH-prostate cancer progression hypothesis. Osteoblastic metastases induce secondary hyperparathyroidism as calcium ions are transferred from serum into blastic bone. Elevated PTH weakens the normal bone, which may already be weakened as the result of androgen deprivation therapy, and promotes the growth of prostate cancer in bone via its mitogenic effects on prostate cancer cells. The growth of blastic metastases establishes a vicious cycle of high PTH, high bone turnover, and increased morbidity and mortality from the consequences of bony remodeling.

androgens (the mainstay of prostate cancer therapy), it may be desirable to suppress serum PTH, either concurrent with androgen suppression or after androgen suppression therapy has failed.

PTH Suppression

Therapeutic options to suppress PTH include vitamin D sterols [e.g., 1,25-dihydroxyvitamin D (calcitriol) and its analogues, 19-*nor*-1,25-dihydroxyvitamin D₂, paricalcitol, and 1 α -vitamin D₂, doxercalciferol], calcimimetics (e.g., cinacalcet), and, for elevated PTH that is refractory to other therapies, parathyroidectomy (49-52). Because cinacalcet lowers serum calcium, its use in prostate cancer would require careful monitoring as prostate cancer patients with bony metastases are at risk of hypocalcemia (22). Conversely, vitamin D sterols cause an increase in serum calcium. Vitamin D sterols are attractive therapeutic candidates because, in addition to suppressing serum PTH, these drugs inhibit the proliferation of prostate cancer cells by multiple mechanisms that do not involve PTH.

Considerable attention has focused on the role of vitamin D in prostate cancer, fueled by the observation

that mortality rates from prostate cancer are inversely related to levels of ultraviolet radiation, the major source of vitamin D (53), and by the demonstration that prostate cancer cells possess high-affinity vitamin D receptor (54). When bound to the vitamin D receptor, 1,25(OH)₂D regulates more than 60 genes that exert prodifferentiating, antiproliferative, and antimetastatic effects on prostate cells through multiple mechanisms (55), including effects on cell cycle, angiogenesis (56) and down-regulation of PTH-related protein expression by prostate cancer cells (57; see refs. 58, 59 for reviews). Several therapeutic trials of calcitriol and its analogues in advanced prostate cancer have been reported with relatively few clinical responses (60). However, in a double-blinded randomized trial of high-dose calcitriol (as DN-101), Beer et al. (ASCENT trial) reported a significant 8-month survival advantage for men with androgen-independent prostate cancer treated with taxane plus calcitriol versus taxane plus placebo (hazard ratio for death, 0.67; ref. 61). It is unknown whether this apparent survival advantage is the result of a direct effect of calcitriol on prostate cancer cells or of an indirect effect on prostate cancer metastases via its suppression of PTH or a combination of these (and other) mechanisms. Understanding the mechanism(s)

that underlie the survival benefit is important because this benefit conceivably could be achieved with lower, potentially less toxic doses of calcitriol/calcitriol analogues as well as by other means (62).

In addition to effects on mortality, suppression of serum PTH in prostate cancer may reduce disease morbidity (e.g., fracture risk and bone pain). Prostate cancer patients are often treated with bisphosphonates, antiresorptive agents that have been shown to reduce the number of skeletal events (63, 64). Bisphosphonates also lower serum calcium, as evidenced by reports of iatrogenic hypocalcemia in prostate cancer patients receiving bisphosphonates (65, 66). Thus, drugs like calcitriol and analogues that suppress PTH without inducing hypocalcemia could play a complimentary or alternative role to bisphosphonates in fracture reduction in prostate cancer, as has recently been proposed for the combination of calcitriol analogues and bisphosphonates in osteoporosis (67).

PTH is a major hormonal determinant of bone resorption. Numerous studies have shown strong correlations between the rate of bone resorption and bone pain (refs. 20, 68, 69). Thus, suppressing PTH in prostate cancer patients with elevated PTH may have a positive influence on bone pain and thereby on health-related quality of life, analogous to the improvement in quality of life in prostate cancer patients receiving androgen deprivation therapy (70). Because several Food and Drug Administration–approved medications for PTH suppression are readily available, their exploration in prostate cancer therapy should be a research priority.

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Prostate Cancer, Serum Parathyroid Hormone, and the Progression of Skeletal Metastases

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