

Quality of Life Questionnaire.

Subjectively, both groups experienced a significant improvement in urgency, and the estradiol group experienced a significant improvement in urge incontinence; however, there were no significant differences between the groups. Objectively, no significant differences were demonstrated between the groups. Nine women in the estradiol group experienced vaginal bleeding, of whom 5 required a hysterectomy during or after the study.

Despite the use of numerous outcome measures, the 25-mg estradiol implant did not produce a greater improvement in urgency symptoms compared with placebo. In addition, the estradiol implant was associated with a high complication rate. These results make it difficult to justify the use of estrogen for overactive bladder symptoms. Although estrogen may play a role in reducing the discomfort and irritation associated with atrophic vaginal tissue, it appears to have no use in the treatment of bladder urgency symptoms.

Relationship Between Patient Report and Physician Assessment of Urinary Incontinence Severity

Melville JL, Miller EA, Fialkow MF, et al.

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How severe is your patient's incontinence? Does a patient know when her urinary incontinence is severe versus mild? The purpose of this study was to determine the relationship between patient report and physician assessment of urinary incontinence severity. A total of 153 women with urinary incontinence completed a detailed health questionnaire that included a medical comorbidity scale, the 12-item short-form health survey (SF-12), the incontinence quality of life instrument, the Primary Care Evaluation of Mental Disorders (PRIME-MD) Patient Health Questionnaire, and a patient incontinence severity assessment. The study was carried out at the University of Washington's Department of Obstetrics and Gynecology in Seattle.

The patient incontinence severity assessment is a single question that asks the patient to rate the severity of her incontinence symptoms on a 5-point Likert scale (range, 1 [mild] to 5 [severe]). In addition, the physicians assigned each patient a physician incontinence severity assessment score, which rates the severity of the patient's incontinence on a 5-point Likert scale (range, 1 [mild] to 5 [severe]).

The study found a high correlation between patient report and physician assessment of urinary incontinence severity. Both patient report (patient incontinence severity assessment) and physician assessment (physician incontinence severity assessment) correlated well with a validated

severity index. The agreement between patient and physician ratings was highest for mild incontinence but decreased as incontinence severity progressed.

Most urologists would likely agree with the conclusions of this study. When symptoms are mild to moderate, the patient history is clear and empiric treatment is often successful. When leakage is severe, it becomes difficult to differentiate between urge and stress incontinence. We have all heard statements such as "I don't know when I leak" or "I leak all of the time." These situations are frustrating for both patients and doctors. Careful patient assessment, including urodynamic evaluation, is most helpful in these instances. ■

Prostate Cancer

Vitamin D for the Management of Prostate Cancer

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Although vitamin D can be obtained from many natural dietary sources, such as fish liver oil, eggs, and dairy products, for the majority of men, this dietary source fails to meet the daily required levels.^{1,2} Instead, their major source of vitamin D is derived from synthesis in the skin through conversion of a precursor (7-dehydrocholesterol) into vitamin D₃, a reaction catalyzed by ultraviolet light present in sunlight.² Vitamin D₃ subsequently undergoes hydroxylation in the liver followed by the kidney, resulting in the synthesis of 1,25-dihydroxyvitamin D₃, or calcitriol, which is the principal active hormonal form of vitamin D.²

In addition to its well-known role in regulating calcium homeostasis in the body via its actions in the kidney, bone, intestine, and parathyroid glands,² vitamin D also exhibits antitumorigenic properties, as demonstrated in in-vivo studies.³ This knowledge has led to epidemiologic studies investigating the association between vitamin D deficiency and prostate cancer. Accordingly, Schwartz and Hulka⁴ were the first to propose that low levels of vitamin D increase the risk of prostate cancer. These observations were based on

prostate cancer mortality rates in the United States, which are inversely related to ultraviolet light exposure. This, in turn, has led to numerous studies investigating the antiproliferative properties of vitamin D on the prostate.⁵⁻⁷

It is now well established that vitamin D, via the induction of cell cycle arrest and/or apoptosis, inhibits the growth of normal prostatic epithelial cells, as well as primary cultures of prostate cancer cells and prostate cancer cell lines.⁵⁻⁷ Although the molecular pathways involved in the antiproliferative action of vitamin D are not well delineated, the cell cycle inhibitor p21^{WAF1/CIP1} and insulin-like growth factor binding protein-3 (IGFBP-3) have been implicated.^{8,9} It has recently been proposed that, beyond its antiproliferative properties, vitamin D harbors antimetastatic potential. This hypothesis is based on the ability of vitamin D to reduce invasion and adhesion of androgen-independent prostate cancer cells lines in vitro,¹⁰ as well as in a xenograft model of rat prostate cancer.¹¹ Because of the toxicity associated with daily administration of vitamin D, weekly administration and use of vitamin D analogs have recently generated great interest. Two recently published papers report on these subjects.

High-Dose Weekly Oral Calcitriol in Patients With a Rising PSA After Prostatectomy or Radiation for Prostate Carcinoma

Beer TM, Lemmon D, Lowe BA, Henner WD.

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Previously, Gross and colleagues¹² investigated the impact of daily oral calcitriol in 7 men with prostate-specific antigen (PSA) recurrence after previous definitive therapy (surgery or radiation). Although a reduction in serum PSA was noted in 6 of 7 subjects, there was predictable development of hypercalcemia and hypercalciuria. In an attempt to avoid these complications, Beer and colleagues investigated the long-term toxicity of weekly oral administration of calcitriol and the impact of this regimen on serum PSA levels in 22 men with biochemical recurrence (median serum PSA, 5.8 ng/mL; range, 1.1-38.6 ng/mL) after radical prostatectomy and/or radiation therapy who did not receive any systemic adjuvant therapy. Calcitriol administration was continued until a maximum of a 4-fold rise in serum PSA level was reached or clinical evidence of disease progression. The primary end point of the study was a PSA response, which was defined as a 50% reduction in serum PSA level confirmed by 2 measurements at least 4 weeks apart. The secondary end point was a statistically significant increase in the PSA doubling time (PSADT). The study cohort received calcitriol for a median duration of 10

months (range, 2-25 months). At the time of publication, 21 of 22 subjects had discontinued treatment because of a variety of factors, including the development of metastatic disease (n = 2), a 4-fold increase in serum PSA level (n = 2), and at the request of their physicians due to rising serum PSA levels that were not 4-fold greater than the baseline values (n = 15). In addition, although no grade 3 or higher toxicity was detected and no patient experienced hypercalcemia or renal calculi, 2 men discontinued therapy because of toxicity (1 due to worsening of preexisting atrial fibrillation and 1 due to elevation in creatinine). Although no subject met the primary end point, 3 men experienced some reduction in serum PSA level (10%-47%) and 3 experienced a significant increase in PSADT. The remaining 16 men had no change in PSADT.

Even with the small study population and the lack of randomization comparing calcitriol with placebo, the results of this study are disappointing. Although moderately well tolerated, calcitriol failed to demonstrate an impact on disease progression. These results may have been related to the selection of the study group itself, the majority of whom most likely harbored aggressive disease; only 10 of the 22 subjects received definitive monotherapy (radical prostatectomy [n = 5] or radiation [n = 5]), whereas the remainder received either neoadjuvant hormonal therapy (n = 4) or adjuvant radiation therapy (n = 8). This explanation for the failed response is further strengthened by the fact that 14 subjects (64%) experienced biochemical recurrence within 2 years of definitive therapy, placing them at an increased risk for developing metastatic disease.¹³ Serum calcitriol levels were measured in 6 subjects and revealed that, within 24 hours of calcitriol administration, there was a sharp decline in its concentration (half-life, 6-11 hours). Therefore, it is possible that serum calcitriol levels become subtherapeutic well before the time for repeat dosing, making this treatment less efficacious.

Growth Inhibition and Differentiation in Human Prostate Carcinoma Cells Induced by the Vitamin D Analog 1 α ,24-Dihydroxyvitamin D₂

Bauer JA, Thompson TA, Church DR, et al.

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In an effort to address the hypercalcemic toxicity associated with vitamin D, there has been a recent growth of interest in vitamin D analogs that are less toxic but retain efficacy as a modality for cancer intervention. To this end, Bauer and colleagues conducted in vitro studies to determine the impact of the less hypercalcemic vitamin D analog 1 α ,24-

dihydroxyvitamin D₂ (1,24-[OH]₂D₂) on cellular growth inhibition and differentiation induction in the androgen-sensitive human prostate cancer cell line LNCaP. Study results revealed that, in the presence of androgen, 1,24-(OH)₂D₂ significantly inhibited the growth of LNCaP cells in a manner that was comparable to vitamin D. Furthermore, 1,24-(OH)₂D₂ was more potent than vitamin D at inducing PSA release from LNCaP cells, suggesting that it may be a more potent differentiating agent. The authors concluded that, with its lower calcemic toxicity compared with vitamin D, 1,24-(OH)₂D₂ may provide a promising vitamin D-based therapeutic modality for prostate cancer. However, before this can be confirmed, the antiproliferative properties of 1,24-(OH)₂D₂ need to be demonstrated in an animal model of prostate cancer (in vivo studies) and subsequently in clinical trials.

In summary, although daily oral administration of vitamin D can inhibit prostate cancer growth, the resultant hypercalcemia precludes regular use of this regimen. Weekly administration has been considered but does not appear to be efficacious. Vitamin D analogs that have less hypercalcemic toxicity may prove to be of benefit in the treatment of prostate cancer. However, it is too early to confirm this. ■

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Finasteride and Prostate Cancer

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Although testosterone is the major circulating androgen in men, dihydrotestosterone (DHT) is more potent and is the major form of androgen found within the prostate gland.¹ DHT, which is responsible for maintaining prostate growth, is produced through reduction of testosterone by an enzyme called 5- α -reductase.¹ DHT is regarded as an extremely important factor in the pathogenesis of benign prostatic hyperplasia (BPH).²

There are 2 isoforms of 5- α -reductase (types 1 and 2). The type 2 enzyme predominates within the prostate and is localized to the fibromuscular stromal compartment.³ Therefore, finasteride, a selective competitive inhibitor of 5- α -reductase type 2, was developed to address the management of BPH.⁴ Accordingly, use of finasteride significantly reduces urinary symptom score, improves urinary flow rates, and reduces prostate volume in men with BPH.²

Like BPH, prostate cancer is known to be androgen-dependent, and finasteride inhibits the proliferation of prostate cancer cell lines both in vitro and in vivo.^{5,6} These findings incited the National Cancer Institute (NCI) and the South West Oncology Group (SWOG) to consider whether finasteride could reduce the risk of prostate cancer. In 1993, a large-scale study of prostate adenocarcinoma chemoprevention with finasteride was initiated: the Prostate Cancer Prevention Trial (PCPT). A recently published paper reports the findings of this important study.

The Influence of Finasteride on the Development of Prostate Cancer

Thompson IM, Goodman PJ, Tangen CM, et al.

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Between January 1994 and May 1997, 18,882 men aged 55 years or older with a normal digital rectal examination (DRE) and a serum prostate-specific antigen (PSA) level of 3.0 ng/mL or lower were randomized to receive either finasteride (5 mg/d) or placebo for 7 years. Prostate biopsy was recommended if the annual serum PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng/mL or if DRE was abnormal. In addition, all men were to be offered an end-of-study biopsy. The authors anticipated that 60% of the participants would have prostate cancer diagnosed during the study or would undergo biopsy at the end of the study. The