Original Article
Phase IIa, randomized placebo-controlled trial of single high dose cholecalciferol (vitamin D₃) and daily Genistein (G-2535) versus double placebo in men with early stage prostate cancer undergoing prostatectomy

David Jarrard¹, Badrinath Konety⁴, Wei Huang³, Tracy Downs¹, Jill Kolesar³,⁸, Kyung Mann Kim⁷,⁸, Tom Havighurst⁷,⁸, Joel Slaton⁴, Margaret G House⁵, Howard L Parnes⁵, Howard H Bailey²,⁸

¹Department of Urology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ²Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ³Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, USA; ⁴Department of Urology, University of Minnesota, Minneapolis, MN, USA; ⁵National Cancer Institute, Bethesda, MD, USA; ⁶Environmental and Molecular Toxicology, University of Wisconsin, Madison, WI, USA; ⁷Department of Biostatistics and Medical Informatics, University of Wisconsin, Madison, WI, USA; ⁸University of Wisconsin Carbone Cancer Center, Madison, WI, USA; ⁹School of Pharmacy, University of Wisconsin, Madison, WI, USA

Received July 18, 2016; Accepted August 18, 2016; Epub September 20, 2016; Published September 30, 2016

Abstract: Introduction and objectives: Prostate cancer (PCa) represents an important target for chemoprevention given its prolonged natural history and high prevalence. Epidemiologic and laboratory data suggest that vitamin D and genistein (soy isoflavone) may decrease PCa progression. The effect of vitamin D on prostate epithelial cell proliferation and differentiation is well documented and genistein may augment this affect through inhibition of the CYP24 enzyme, which is responsible for intracellular vitamin D metabolism. In addition, both genistein and vitamin D inhibit the intraprostatic synthesis of prostaglandin E2, an important mediator of inflammation. The objectives of this prospective multicenter trial were to compare prostate tissue calcitriol levels and downstream related biomarkers in men with localized prostate cancer randomized to receive cholecalciferol and genistein versus placebo cholecalciferol and placebo genistein during the pre-prostatectomy period. Methods: Men undergoing radical prostatectomy were randomly assigned to one of two treatment groups: (1) cholecalciferol (vitamin D₃) 200,000 IU as one dose at study entry plus genistein (G-2535), 600 mg daily or (2) placebo cholecalciferol day 1 and placebo genistein PO daily for 21-28 days prior to radical prostatectomy. Serum and tissue analyses were performed and side-effects recorded. Results: A total of 15 patients were enrolled, 8 in the placebo arm and 7 in the vitamin D₃ + genistein (VD + G) arm. All patients were compliant and completed the study. No significant differences in side effect profiles were noted. Utilization of the VD + G trended toward increased calcitriol serum concentrations when compared to placebo (0.104 ± 0.2 vs. 0.0013 ± 0.08; p=0.08); however, prostate tissue levels did not increase. Calcidiol levels did not change (p=0.5). Immunohistochemistry for marker analyses using VECTRA automated quantitation revealed an increase in AR expression (p=0.04) and a trend toward increased TUNEL staining (p=0.1) in prostate cancer tissues in men randomized to receive VD + G compared to placebo. Conclusions: In this first study testing the combination of a single, large dose of cholecalciferol and daily genistein, the agents were well tolerated. While an increase in AR expression suggesting differentiation was observed, it is difficult to draw firm conclusions regarding the bioactivity of the combination given the sample size.

Keywords: Cholecalciferol, genistein, active surveillance, prostate cancer

Introduction
Prostate cancer is the most common malignancy and the second leading cause of cancer-related death [1]. Due to its long natural history and the low proportion of deaths to cancer prevalence, prostate cancer represents an excellent target for chemoprevention [2, 3]. While a number of chemopreventive agents are under investigation [4], only 5α-reductase inhibitors such as finasteride or dutasteride have shown a significant benefit [5, 6]. Multiple studies have shown that vitamin D has activity in prostate cancer both in vitro and in...
Vitamin D and genistein prostate chemoprevention

vivo [7]. Upon ingestion, cholecalciferol (vitamin D$_3$) is eventually metabolized to calcitriol (1,25-dihydroxyvitamin D$_3$), which binds to the intracellular vitamin D receptor (VDR), heterodimerizes with the retinoid X receptor, and binds DNA [8, 9]. The resulting protein transcription results in net increase in circulating calcium and phosphorus by increasing intestinal absorption and mobilization from bone, and decreasing urinary excretion [9, 10]. Other tissues (including prostate epithelial cells) contain vitamin D receptors (VDRs), providing a mechanistic basis for its potential chemopreventive activity [11]. Epidemiological evidence has suggested chronic sunlight exposure reduces risk of prostate cancer, but a clear association between serum vitamin D$_3$ levels and reduced risk is less clear suggesting other factors play a role [12, 13]. Furthermore, specific VDR polymorphisms are associated with increased risks of prostate cancer [14].

Cholecalciferol plays an important role in the development and differentiation of normal epithelia, including prostate [15]. Human prostate epithelial cells metabolize cholecalciferol to calcitriol particularly in the peripheral zone of the prostate, which is where 70% of prostate cancers originate [7, 15]. Calcitriol has been shown to inhibit in vivo growth and invasion, and induce differentiation in prostate cancer cells [16-20]. In addition, it has been shown to inhibit proliferation (Ki67) [21] and induce apoptosis (TUNEL, increased caspase 3) [22, 23]. Furthermore, calcitriol modulates expression of p21 [24], prostaglandin-E$_2$ (PGE$_2$) [25], cyclooxygenase-2 (COX-2) [26], and the insulin growth factors axis [25, 26].

Several trials with vitamin D$_2$ and vitamin D$_3$ in hormone-resistant prostate cancer have resulted in some decreases in prostate specific antigen (PSA) levels and lengthening of median survival with the addition of calcitriol to docetaxel chemotherapy in men with advanced prostate cancer [27-30]. However, investigations of calcitriol as a cancer therapy have been limited by toxicity [29]. Treatment with cholecalciferol is safer since it can be converted to calcitriol by prostate cells without generating systemic hypercalcemia [2]. In fact, a 100,000 IU dose of cholecalciferol in 30 adults increased blood levels from a mean of 27.1 ± 7.7 ng/ml at baseline to a mean of 42 ± 9.2 ng/ml after four months, and was found to be safe [30]. Another strategy to reduce the risk for hypercalcemia caused by vitamin D is to use low doses in combination with other cancer prevention agents. This was investigated previously in an NCI, DCP-sponsored phase IIa trial comparing cholecalciferol with and without calcium carbonate, and calcitriol alone in subjects with previous colorectal adenomas. However, no effects on various biomarkers were found after six months.

Genistein is one of the main isoflavone glycoside conjugates found in soybeans [31]. Epidemiological studies have suggested that consumption of soybean-based products are linked to reduced risk for developing prostate and other cancers [32]. The efficacy of soy and genistein in the setting of prostate cancer chemoprevention clinical trials has been mixed [33-35]. Genistein-induced morphologic changes in prostate carcinoma cell lines have been linked to in vitro genistein-induced cell attachment to the substratum [36]. Genistein is known to modulate a number of proteins implicated in prostate carcinogenesis and vitamin D metabolism including expression of CY-P24 and CYP27B1 [35, 36], COX-2 activity [24, 37], PGE$_2$ [38] and PGF2a receptor [39], histone deacetylase (HDAC) [40], heat shock protein (Hsp) [41], and Hsp90 chaperone activity [42].

A recent study combining calcitriol and genistein showed synergistic activity against prostate cancer cells in vitro [43]. Genistein appears to enhance calcitriol activity in PC3 cells due to inhibition of COX-2, CYP24 and CYP27B1 enzymes, which are important in calcitriol degradation [44]. The addition of genistein to cholecalciferol may thus extend the half-life of calcitriol, increase calcitriol tissue levels and potentiate inhibition of the prostaglandin pathway. In the current study, we assessed the effect on vitamin D prostate tissue levels of calcitriol and downstream vitamin D-related biomarkers, of adding daily genistein to a single, large dose of cholecalciferol in patients awaiting radical prostatectomy for localized prostate cancer.

Material and methods

Trial design

The trial was performed utilizing the University of Wisconsin chemoprevention consortium (UWCCC CO10805/UW109-14-01) and consisted of 4 sites: The Universities of Wisconsin-Madison, Minnesota, and Alabama-Birmingham.
Vitamin D and genistein prostate chemoprevention

**SCHEMA**

Phase IIa, randomized placebo controlled trial of single high dose cholecalciferol and daily genistein (G-2535) versus placebo in men with early stage prostate cancer undergoing prostatectomy

Patients found to have clinically localized prostate cancer and are candidates for subsequent radical prostatectomy

↓

Eligibility confirmation, safety labs blood biomarkers and pharmacokinetics*

↓

Participants will be randomized in equal numbers to one of two treatment arms

<table>
<thead>
<tr>
<th>Arm I</th>
<th>Arm II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholecalciferol 200,000 IU (four 50,000 IU capsules) po on Day 1 only</td>
<td>Cholecalciferol Placebo (four placebo capsules matching cholecalciferol) po on Day 1 only</td>
</tr>
<tr>
<td>and</td>
<td>and</td>
</tr>
<tr>
<td>Two G-2535 capsules (to provide 600 mg of genistein) taken together, po daily x 21-28 days.</td>
<td>Two placebo capsules matching G-2535, taken together, po, daily x 21-28 days.</td>
</tr>
</tbody>
</table>

↓

Pre-prostatectomy labs, blood biomarkers and pharmacokinetics* done before surgery

↓

RADICAL PROSTATECTOMY

↓

Prostate tissue collected for biomarkers and pharmacokinetics**

* Biomarkers: plasma, PSA, IGF-1, IGF-2, IGFBP-3, IGFBP3 ratio; Biomarkers: serum: calcium, PTH DNA from Paxgene, CYP24 and CYP27B1 SNPs PBMC CYP mRNA expression: CYP24, CYP27B1 Pharmacokinetics, plasma: Genistein, daidzein Pharmacokinetics, serum: cholecalciferol, calcidiol, calcitriol, calcitric acid

** Biomarkers: VDR, AR, Ki-67, TUNEL, caspase 3, PGE2, IGF-1 and IGF-2, p21, Akt, phosphorylated Akt, PSMA staining, MIS, CYP mRNA expression: CYP24, CYP27B1 Pharmacokinetics: Calcitriol, Calcidiol, calcitric acid, genistein and daidzein

Figure 1. Study schema.
Vitamin D and genistein prostate chemoprevention

and biomarker analyses. The evening before surgery the patient took the final dose of study drug and on the morning before their prostatectomy, (approximately twelve hours after the last dose of study drug) adverse events and biomarker evaluations were performed and remaining study drug/placebo collected. The primary objective of the study was to determine the change (day 0 to day end of study) in serum 25-OH-vitamin D (calcidiol) and tissue 1,25-OH-vitamin D (calcitriol). Secondary objectives included serum levels of calcitriol, calcium, parathyroid hormone, IGF-1, IGF-2, IGFBP-3 and PSA. Others included tissue expression of VDR, androgen receptor, prostate specific membrane antigen (PSMA); COX-2, TUNEL staining (apoptosis), caspase 3 (apoptosis), Ki-67 (proliferation), PGE$_2$, Akt, phosphorylated Akt, p21, IGF-1 and IGF-2.

Serum/plasma biomarkers

Serum or plasma levels of calcium, parathyroid hormone, IGF-1, IGF-2 and IGFBP-3, 1,25(OH)$_2$D (calcitriol) and 25-OH-D (calcidiol) were assessed at baseline, and the day of prostatectomy (prior to surgery). Calcidiol and calcitriol were measured with enzyme immunoassays using commercial kits (Immunodiagnostics Systems and MD Biosciences) as previously described [45]. The lower limit of quantization is 0.28 ng/mL for calcitriol, and 4.0 ng/mL for calcidiol, with intra- and inter-day variability of less than 15%. IGF-1, IGF-2, IGFBP-3, PSA levels were measured by a commercially available sandwich immunoassay (Quantikine human, R&D Systems, Minneapolis, MN, Genistein and diadzein concentrations were analyzed in plasma as previously described by King et al. [46]. Briefly, samples were analyzed by a validated reversed phase HPLC assay. The lower limit of quantization is 3.9 ng/mL for genistein, and 3.1 ng/mL for daidzein, with intra- and inter-day variability of less than 15%.

Tissue biomarkers and immunohistochemical VECTRA analysis

Frozen tissue was collected and stored at -80°C, then eventually thawed at room temper-
Vitamin D and genistein prostate chemoprevention

Table 2. Adverse events

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=8)</th>
<th>Vitamin D₂ + genistein (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (%)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>1 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>1 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Sinus pain</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>0 (0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are number of patients (%). Adverse events shown here have a frequency of 15% or higher in either treatment arm or are graded as moderate (CTCAE grade 2) or severe (CTCAE grade 3).

Results

Men with a histologic diagnosis of prostate cancer scheduled for radical prostatectomy were eligible for this study and clinicopathologic data is detailed in Table 1. Subjects were randomly assigned to one of two treatment groups: (1) cholecalciferol, 200,000 IU p.o. as one dose on day 1 plus genistein, 600 mg p.o. daily or (2) placebo cholecalciferol day one and placebo genistein daily for 21-28 days prior to radical prostatectomy. The study design is detailed in Figure 1. We have found in prior studies that the perception of delayed surgery is a significant disincentive to enrollment and therefore offered the 21-28 day treatment option.

Statistical methods

The primary analysis was a comparison of tissue levels of calcitriol between the placebo group and the cholecalciferol/genistein group using Student t-test. If the normality assumption was tenuous, an appropriate transformation of the data such as logarithm was considered or a nonparametric test such as Wilcoxon rank-sum test was used for comparison. The lower limit of detection (LLOD) for tissue calcitriol was 0.28 ng/mL; samples below this levels were recorded as 0. Secondary endpoints were summarized by treatment arm with descriptive statistics and analyzed using two-sample Wilcoxon rank-sum tests. P-values < 0.05 were considered statistically significant without adjustment for multiple tests.

Sample size justification

Sample size was estimated based on a two-sample t-test to detect calcitriol tissue concentration differences at a two-sided significance level of 0.05 between active and placebo. The goal was to recruit 50 participants, or 25 participants in each treatment arm; after dropout (which, in our experience with comparable studies has been less than 7%) we expected to have an effective sample size of 23 participants in each treatment arm, or 46 participants. With an effective sample size of 46, the trial would have had a power between 0.77 and 0.92 to detect an effect size between 0.8 to 1.

Sample preparation and antigen retrieval were conducted as previously described [48]. Briefly, the slides were taken through routine deparaffinization and rehydration. Two triple stains were performed on sections using antibodies to VDR; androgen receptor; prostate specific membrane antigen (PSMA, R&D Systems); TUNEL staining (apoptosis, Trevigen Inc); Caspase 3 (apoptosis, Cell Signaling Technology Inc.); Ki-67 (proliferation); Akt (404D, Cell signaling Technology Inc); p21 (EA10, Abcam Inc); IGF-1 (7973, Abcam Inc) and IGF-2 (9574, Abcam Inc). E-cadherin antibodies (Cell Signaling Technology, Beverly, MA) were used to define the epithelial compartment for better tissue segmentation. Cores with <5% epithelial component or loss of tissue were excluded from the analysis. Per-cell protein target signals were quantitated for individual cores using the VECTRA™ imaging system according to manufacturer's protocols (Caliper Life Sciences, Hopkinton, MA). The inForm 1.2TM software was used to segment tissue subcellular compartments (nucleus vs. cytoplasm) and tissue compartments (epithelium vs. stroma).
A total of 15 patients were enrolled, 8 in the placebo arm and 7 in the vitamin D + genistein (VD + G) arm. All patients were compliant and completed the study, however missed doses occurred in 1 (12%) and 2 (28%) of the placebo and VD + G groups respectively. Adverse events occurred in 4 patients in the placebo group and 5 from the VD + G group (Table 2). One patient in the placebo arm developed severe hypophosphatemia that was deemed possibly related to the study drug.

Serum and tissue biomarkers and chemistries were performed. Analysis of the primary study endpoint, prostate tissue calcitriol levels, did not significantly differ between the two groups (p=0.92). Tissue calcitriol was detectable in only 1/7 patients on VD + G compared to 1/8

Table 3. Calcitriol levels in tissue and serum

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>Placebo (n=8)</th>
<th>Vitamin D₃ + genistein (n=7)</th>
<th>p-value</th>
<th>All (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue calcitriol (ng/mL)†</td>
<td>0 (0-0.358)</td>
<td>0 (0-0.396)</td>
<td>0.92</td>
<td>0 (0-0.396)</td>
</tr>
<tr>
<td>Serum calcitriol, baseline (ng/mL)</td>
<td>0.517 ± 0.124</td>
<td>0.531 ± 0.201</td>
<td>0.60</td>
<td>0.523 ± 0.158</td>
</tr>
<tr>
<td>EOS (ng/mL)</td>
<td>0.518 ± 0.143</td>
<td>0.654 ± 0.355</td>
<td>0.22</td>
<td>0.576 ± 0.254</td>
</tr>
<tr>
<td>Change (ng/mL)</td>
<td>0.0013 ± 0.076</td>
<td>0.104 ± 0.149</td>
<td>0.08</td>
<td>0.0454 ± 0.120</td>
</tr>
<tr>
<td>Serum calcidiol, baseline (ng/mL)</td>
<td>20.5 ± 5.50</td>
<td>24.5 ± 9.3</td>
<td>0.60</td>
<td>22.4 ± 7.5</td>
</tr>
<tr>
<td>EOS (ng/mL)</td>
<td>19.2 ± 5.10</td>
<td>27.3 ± 10.0</td>
<td>0.14</td>
<td>22.7 ± 8.4</td>
</tr>
<tr>
<td>Change (ng/mL)</td>
<td>-1.40 ± 5.30</td>
<td>0.8 ± 12.6</td>
<td>0.56</td>
<td>-0.4 ± 8.8</td>
</tr>
</tbody>
</table>

*Presented as number (percentage) or mean ± SD; †Only one nonmissing observation in each arm; presented as median and range.

Figure 2. Absolute changes in serum calcitriol and serum calcidiol at the end of study. Participants were randomly assigned to cholecalciferol, 200,000 IU p.o. on day 1 plus genistein, 600 mg p.o. daily or Placebo cholecalciferol on day one and placebo genistein daily for 21-28 days prior to radical prostatectomy. Serum was drawn the morning of surgery and analyzed as described in methods. (A) Serum Calcitriol levels (p=0.08) and (B) serum Calcidiol levels (p=0.56) in the drug versus control groups.
Vitamin D and genistein prostate chemoprevention

on placebo. Participants receiving active VD + G showed a trend toward increased serum calcitriol (p=0.08, Table 3, Figure 2) but the compounds did not significantly effect serum calcidiol (e.g. 25-OH-vitamin D; p=0.5) the most standard measure of vitamin D status, when compared to placebo. Serum TSH did show a trend toward decreasing in the VD + G group from baseline to a greater extent than placebo (p=0.055), but levels between the groups did not differ. Serum T₄ was not altered.

Figure 3. Analysis of TUNEL and androgen receptor expression. Prostate tissues were collected at the time of radical prostatectomy and paraffin embedded samples were subjected to immunohistochemistry as described. Vectra™, an automated quantitative system was utilized for analysis. Androgen Receptor (AR) in benign (A) and cancer (B) tissues. TUNEL expression, a marker of apoptosis, is demonstrated in benign (C) and cancer tissues (D). P values are documented.

Immunostaining for tissue biomarkers including the apoptosis markers Caspase 3, PSMA, IGF-1, IGF-2, Akt, p21, PGE₂ and others was performed as described and included all samples. Vectra™ automated quantitative analysis was performed which permits tissue segmentation focusing on the epithelial component and quantitation of the nuclear-cytoplasmic portion. Given the small patient numbers, limited conclusions were able to be drawn when comparing the placebo and VD + G groups. A trend toward greater TUNEL staining in the nucleus was found in the VD + G arm in the prostate cancer tissue samples (p=0.16) (Figure 3). Interestingly, AR expression in the nucleus was greater in the VD + G group relative to placebo in prostate cancer samples (p=0.041) but not in benign tissues (p=0.4).

Discussion

In this consortium study, the primary objective of this study was to determine differences in prostate tissue steady state concentrations of
calcitriol in participants treated with a single dose cholecalciferol (200,000 IU) and G-2535 (which provides 600 mg of genistein) versus those receiving placebo. Only one patient on each study arm had measurable levels of calcitriol in prostate tissue indicating that the active form of the vitamin did not readily accumulate in the prostate with these doses. However, significant differences in serum calcidiol levels were not observed on the two study arms (p=0.5), suggesting that we may not have adequately tested the primary study hypothesis. Preliminary data has observed genistein inhibiting the expression of CYP24 (24-hydroxylase) with resultant greater growth inhibitory effects of calcitriol in prostate tissue [44]. The combination of high dose vitamin D plus genistein was therefore postulated to result in greater prostate tissue concentrations of calcitriol than with vitamin D alone. The number of patients enrolled in the trial adversely impacted the statistical analyses making a definitive conclusion difficult.

A secondary objective of this study was to assess the effect of adding genistein to patients receiving a single dose of cholecalciferol on the modulation of vitamin D-related biomarkers in patients undergoing radical prostatectomy for localized prostate cancer. Several interesting observations were made potentially due to genistein intake. Both cholecalciferol and genistein have been shown to inhibit the growth of prostate cancer in vitro and in vivo and to induce apoptosis with caspase activation. In addition, genistein has been shown to prolong the bioavailability of cholecalciferol. Ki-67 as a marker of proliferation did not differ between groups. TUNEL staining and caspase 3 expression was measured to determine if combination therapy with both agents induces apoptosis in human prostate tissue. A trend toward increased apoptosis was noted in VD + G tumor samples (p=0.16) for TUNEL in the nucleus.

Cholecalciferol can modulate serum expression of PTH, IGF-1/-2, and IGFBP-3 and tissue expression of VDR, androgen receptor, expression of PSMA, prostaglandin, p21, and IGF-1/-2. Genistein can also inhibit vitamin D hydroxylases CYP24 and CYP27B1. Each of these parameters was assessed in this study and no differences noted.

AR signaling plays a pivotal role in prostate cell growth, differentiation and function and is a major focus of interventions in prostate cancer treatment. Quantitative immunohistochemistry demonstrated greater AR expression in PCa treated with VD + Gen relative to placebo (p=0.041) (Figure 2). This was not seen in benign prostate tissues. Previous work has demonstrated that genistein activates AR-driven gene transcription in prostate cancer cells at low concentrations by activating the Raf-MEK-ERK kinase pathway [49], an effect that is reversed at high genistein doses in the rat prostate [50]. The effects of genistein may also depend on the mutational status of the AR [51].

Conclusions

In this feasibility study testing the combination of cholecalciferol and genistein, a trend for increased calcitriol levels was noted in the serum, but not tissue. While an increase in apoptosis and AR expression was observed, it is difficult to draw firm conclusions regarding the bioactivity of the combination given the small sample size and multiple comparisons performed. The finding of no increase in calcidiol levels suggests a sufficient dose of cholecalciferol may not have been applied to test the hypothesis that genistein would augment its effect at the tissue level.

Acknowledgements

Supported by: NIH N01 (CN35156).

Address correspondence to: Dr. David Jarrard, Department of Urology, University of Wisconsin School of Medicine and Public Health, Madison, WI 53792, USA; Environmental and Molecular Toxicology, University of Wisconsin, Madison, WI 53792, USA; University of Wisconsin Carbone Cancer Center, Wisconsin Institute for Medical Research, 1111 Highland Avenue, Madison, WI 53792, USA. Tel: 608-252-0937; Fax: 608-265-0614; E-mail: jarrrard@urology.wisc.edu

References

Vitamin D and genistein prostate chemoprevention


can Urological Association. Use of Saltphe-reductase inhibitors for prostate cancer chemopreven-
tion: American Society of Clinical Oncology/Ameri-


[18] Chen TC, Schwartz GG, Burnstein KL, Loke-


[22] Guzey M, Kitada S, Reed JC. Apoptosis induc-


Vitamin D and genistein prostate chemoprevention


Vitamin D and genistein prostate chemoprevention


