Diet and Dietary Supplement Intervention Trials for the Prevention of Prostate Cancer Recurrence: A Review of the Randomized Controlled Trial Evidence

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Purpose: We review the effect of diet and dietary supplement interventions on prostate cancer progression, recurrence and survival.

Materials and Methods: A literature search was conducted in MEDLINE®, EMBASE® and CINAHL® to identify diet and dietary supplement intervention studies in men with prostate cancer using prostate specific antigen or prostate specific antigen doubling time as a surrogate serum biomarker of prostate cancer recurrence and/or survival.

Results: Of the 32 studies identified 9 (28%) were randomized controlled trials and the focus of this review. In these studies men had confirmed prostate cancer and elevated or increasing prostate specific antigen. Only 1 trial included men with metastatic disease. When body mass index was reported, men were overweight or obese. A significant decrease in prostate specific antigen was observed in some studies using a low fat vegan diet, soy beverage or lycopene supplement. While not often reported as an end point, a significant increase in prostate specific antigen doubling time was observed in a study on lycopene supplementation. In only 1 randomized controlled trial in men undergoing orchietomy was a survival end point of fewer deaths with lycopene supplementation reported.

Conclusions: A limited number of randomized controlled trials were identified in which diet and dietary supplement interventions appeared to slow disease progression in men with prostate cancer, although results vary. Studies were limited by reliance on the surrogate biomarker prostate specific antigen, sample size and study duration. Well designed trials are warranted to expand knowledge, replicate findings and further assess the impact of diet and dietary supplement interventions on recurrence and treatment associated morbidities.

Key Words: diet, dietary supplements, prostatic neoplasms, recurrence

In North America prostate cancer is the most common cancer in men. There are 22,300 men diagnosed annually in Canada1 and 186,295 estimated in 2008 in the United States, representing 25% of all cancers in men.2 Approximately 1 in 8 men will be diagnosed in their lifetime while 1 in 27 will die of the disease.3 The prostate cancer survival rate is high2 and it is often curable by surgery or radiotherapy when confined to the gland. However, approximately 25% to 40% of patients may have recurrence within 5 years.3 The high incidence of prostate cancer coupled with a long latency period affords a particularly attractive target for dietary and lifestyle interventions, especially since conventional treatments are often associated with considerable morbidity such as urinary or bowel dysfunction, impotence, fatigue, weight gain, muscle loss and osteoporosis.4

There is a large variation in prostate cancer rates worldwide5 and migration studies show that cancer rates increase in men who immigrate to the United States,6,7 suggesting an important role of environmental factors including diet in primary prevention. Environmental factors have also been speculated to be important in prostate cancer progression. The rationale and role of diet and dietary supplements in delaying or preventing prostate cancer progression and/or recurrence are well documented in recent reviews that have examined an increasing body of evidence from preclinical and epidemiological studies, and clinical trials.8–11 Furthermore, data on diet related factors such as obesity show a strong association with prostate cancer and worse overall outcomes.12 This early evidence suggests that nontoxic dietary, lifestyle and/or naturally derived interventions could potentially decrease the risk of prostate cancer recurrence and improve survival as well as reduce significant treatment associated morbidity and ameliorate many of the common side effects.

Prior reviews of diet (including body weight), dietary supplements and prostate cancer have focused primarily on evidence from in vitro, in vivo and epidemiological studies with limited use of RCTs.8–12 Therefore, we provide a comprehensive evaluation of diet and dietary supplement inter-
ventions in men with prostate cancer and their respective impact on disease recurrence, progression and survival, with a focus on RCTs. Strengths and gaps in the literature are identified to facilitate further research in this area.

METHODS

A literature search in MEDLINE, EMBASE and CINAHL from 1996 to August 2007 was conducted using the search terms diet, diet therapy, dietary, nutrition, food, macronutrients (fat, carbohydrate, protein), fruits and vegetables, fiber, dietary supplements (herbal, extracts, naturopathic, nutrients, vitamins and minerals, supplements, functional foods, nutraceuticals, antioxidants, micronutrients) and prostate cancer or neoplasm (recurrence, relapse, progression, survival, prognosis). Additional trials were identified from the Natural Medicine Comprehensive Database and bibliographies of relevant articles. Studies included in the review were limited to human trials published in English. However, evidence from RCTs was given precedence because of the rigorous design.

Dietary intervention trials evaluated a comprehensive diet (eg plant based diet), 1 or more macronutrients (eg fat) or a whole food or beverage. In contrast, dietary supplement trials were defined according to Health Canada’s Natural Health Product Directorate definition of vitamins and minerals, herbal remedies, homeopathic medicines, traditional medicines such as traditional Chinese medicines, probiotics, and other products like amino acids and essential fatty acids. Dietary supplements that were used in trials also containing a diet or food were classified and discussed as a combined diet and supplement trial.

An end point of this review was PSA as a surrogate serum biomarker of prostate cancer progression or recurrence. PSA was reported as absolute (total or free) and/or by its change with time, most often as the rate of increase or PSADT. Survival end points were also included in this review when available. Other secondary trial findings, such as proliferation and apoptotic indices, serum sex hormones and others, were not included in the review.

RESULTS

The literature search identified 206 references published in MEDLINE, EMBASE and CINAHL since 1995. Case reports, reviews, preclinical studies, epidemiological studies and primary prevention trials were excluded from study. The herbal mixture PC-SPES was not included in this review because it was recalled in January 2002. A number of other agents such as all-trans retinoic acid, cholecalciferol and calcitriol, which are recognized as vitamin derivatives but available only by prescription, were similarly excluded from study. Finally, along with studies identified from relevant bibliographies and other databases, this search resulted in a data set of 32 studies (tables 1 and 2). Trials were classified into the categories of diet (17), which includes trials with a combined diet and dietary supplement intervention, and dietary supplements (15). A meta-analysis of the studies was not performed due to the heterogeneity of the trials and the diversity of the compounds studied.

We focused on trials with an RCT design, of which there were 9 (28%) with a placebo or control arm (table 1). The remaining 23 trials were nonrandomized and uncon-
Table 1. Summary of PSA end points for RCTs

<table>
<thead>
<tr>
<th>References</th>
<th>Intervention</th>
<th>Subjects and Design</th>
<th>PSA Findings and Significance</th>
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<tr>
<td>Dalais et al\textsuperscript{16}</td>
<td>Phytoestrogen-rich diet: Soy grits (50 gm) or soy grits (50 gm) plus flaxseed (20 gm), wheat control</td>
<td>Men with prostate Ca awaiting prostatectomy\textsuperscript{261} such as soy (8), soy and flaxseed (10), wheat (8); randomized, placebo controlled double blind clinical trial; intervention: 22–27 days; followup: none</td>
<td>PSA: statistically significant difference in % change between soy and placebo (12.7% vs 40.7% (p = 0.021)) based on a decrease from 7.16 ± 3.23 to 6.34 ± 3.05 ng/ml for soy compared to an increase from 5.81 ± 3.70 to 7.11 ± 4.25 ng/ml in control; statistical analysis of flaxseed controlled to control not reported. PSADT: not available</td>
</tr>
<tr>
<td>Kumar et al\textsuperscript{17}</td>
<td>Phytoestrogen-rich diet: Soy protein beverage (60 gm protein)\textsuperscript{6} and 60 mg genistein</td>
<td>Men with prostate Ca on watchful waiting (59): soy (29), placebo (30); randomized, placebo controlled double blind clinical trial; intervention: 12 wks; followup: none</td>
<td>PSA: no difference in mean change in total PSA between soy and placebo based on 7.38 ± 5.62 to 6.77 ± 4.96 ng/ml for soy and 7.45 ± 5.36 to 6.89 ± 5.47 ng/ml for placebo ((p = 0.09)) or free PSA ((p = 0.13)). PSADT: not available</td>
</tr>
<tr>
<td>Bylund et al\textsuperscript{15}</td>
<td>Phytoestrogen-rich diet: Rye bran bread (285 gm), wheat control (275 gm)</td>
<td>Men with prostate Ca on no active treatment (18): bran (10), placebo (8); randomized, placebo controlled single blind pilot study; intervention: 3 wks; followup: none</td>
<td>PSA: no difference in the mean change between rye and placebo based on 14.8 ± 9.1 to 14.7 ± 9.0 ng/ml for rye and 13.2 ± 10.9 to 13.2 ± 10.1 ng/ml for placebo ((p = 0.05)). PSADT: not available</td>
</tr>
<tr>
<td>Parsons et al\textsuperscript{21,23}</td>
<td>Plant based diet: 7 servings vegetables (2 cruciferous, 2 tomato products and 3 other vegetables), 2 servings whole grains, 1 serving legumes</td>
<td>Men with prostate Ca on active surveillance alone (4), plant based diet (29), control (13) or combined with men who completed primary treatment (69)\textsuperscript{23}; plant based diet (45), control (24); intervention: 6 mos; followup: none</td>
<td>PSA (secondary end point): no difference between men who completed primary treatment (no values provided). PSADT: not available</td>
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Combined diet and dietary supplement trials

<table>
<thead>
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<th>References</th>
<th>Intervention</th>
<th>Subjects and Design</th>
<th>PSA Findings and Significance</th>
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<tr>
<td>Ornish et al\textsuperscript{24}</td>
<td>Low fat (10% total calories) vegan diet: soy (1 serving tofu and 58 gm protein); fish oil (3 gm); vitamin E (400 IU); selenium (200 mcg); vitamin C (2,000 mg); stress reduction, exercise and group support</td>
<td>Men with prostate Ca on watchful waiting (90): intervention (41), control (49); randomized, controlled clinical trial; intervention: 12 mos; followup: none</td>
<td>PSA: Statistically significant difference in the mean change between intervention and control (~4% vs 6%, (p = 0.016)) based on a decrease from 6.23 ± 1.7 to 5.98 ± 1.7 ng/ml for intervention compared to an increase from 6.36 ± 1.7 to 6.74 ± 2.1 ng/ml in the control group ((p = 0.001)); unclear if the analysis represents a comparison in the difference in mean change in PSA between groups or before and after analysis. PSADT: not available</td>
</tr>
<tr>
<td>Krane et al\textsuperscript{16}</td>
<td>Margarine (20 gm) containing vitamin E (50 mg), selenium (200 mcg), green tea (6 cups), isoflavones (100 mg), lutein (10 mg), lycopene (10 mg), carotenoids (10 mg)</td>
<td>Men with prostate Ca with increasing PSA after primary treatment or watchful waiting (32): Group 1 (15), Group 2 (17); randomized, placebo controlled, double-blind, 2-arm crossover study; intervention: 8 wks; followup: 8 wks after period 2 intervention</td>
<td>PSA: statistically significant difference between the lycopene group compared with orchiectomy alone based on 9.02 ± 7.5 and 3.01 ± 1.9 ng/ml ((p = 0.001)); unclear if the analysis represents a comparison in the difference in mean change in PSA between groups or before and after analysis. PSADT: not available</td>
</tr>
<tr>
<td>Ansari and Gupta\textsuperscript{21}</td>
<td>Lycopene (4 mg)</td>
<td>Men with metastatic prostate Ca (54), lycopene supplement and orchietomy (27), and orchietomy alone (27); randomized controlled clinical trial; intervention: 2 yrs; followup: none</td>
<td>PSA: no difference in mean % change between lycopene and placebo (~18% vs 14%) based on 6.89 ± 0.81 to 5.64 ± 0.87 ng/ml for lycopene supplements and 6.74 ± 0.88 to 7.65 ± 1.78 ng/ml for placebo ((p = 0.25)). PSADT: not available</td>
</tr>
<tr>
<td>Kucuk et al\textsuperscript{19}</td>
<td>Lycopene (30 mg)</td>
<td>Men with prostate Ca awaiting surgery (261): lycopene (15), control (11); randomized, placebo controlled phase II clinical trial; intervention: 3 wks; followup: 13–30 days</td>
<td>PSA: no statistically significant difference in total ((p = 0.076)) or free PSA ((p = 0.988)) PSA between lycopene and placebo controlled in free PSADT based on 1,150 vs 445 days (2.6-fold, (p = 0.041)) for the supplement vs control treated periods; no statistically significant difference observed in the intent to treat group ((p = 0.089)); no statistically significant carryover effect reported ((p = 0.131)).</td>
</tr>
<tr>
<td>Schroder et al\textsuperscript{20}</td>
<td>Soy isoflavones (62.5 mg), lycopene (15 mg), silymarin (160 mg), ascorbic acid (225 mg), α-tocopherol (75 mg), carotenoids (3 mg), bioflavonoids (19 mg), selenium (128 mcg), zinc (18 mg), calcium carbonate (1,148 mg), other</td>
<td>Men with prostate Ca with increasing PSA after primary treatment (42): Group 1 (22), Group 2 (20); randomized, placebo controlled double blind crossover study; intervention: 10 wks followed by 4-wk washout period prior to crossover; followup: none</td>
<td>PSA: no statistically significant difference in % change between lycopene and placebo (12.7% vs 40.7% (p = 0.021)) based on a decrease from 7.16 ± 3.23 to 6.34 ± 3.05 ng/ml for soy compared to an increase from 5.81 ± 3.70 to 7.11 ± 4.25 ng/ml in control; statistical analysis of flaxseed controlled to control not reported. PSADT: not available</td>
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</table>

Followup reported as time from the end of the intervention where relevant.
* Number of subjects reported as 28.
† Mean change in PSA from the manuscript data was calculated to be 11.4% vs 22.4%.
‡ Kumar, personal communication.

Epidemiological studies, including migration studies and reports of lower prostate cancer rates in Asian men with higher soy intakes. In this review the 3 dietary soy trials were conducted in men awaiting prostatectomy\textsuperscript{16} or on watchful waiting,\textsuperscript{17,24} using PSA (rather than PSADT) as the primary end point. A diet supplemented with soy grits for 22 to 27 days significantly decreased PSA by 12.7% compared to a 40% increase in 26 controls,\textsuperscript{16} while an 8.3%
nonsignificant decrease in PSA was observed with a soy beverage for 12 weeks compared to a 7.5% decrease in 59 controls. In the third study a 4% decrease in PSA vs a 6% increase in controls was reported when soy (tofu and soy protein) was combined with a low fat vegan diet, dietary supplements and lifestyle interventions in a 1-year trial.

In the study by Dalais et al flaxseed was combined with soy in one arm of the intervention. However, there was no statistical analysis reported compared to placebo to determine its effect on PSA. Furthermore, PSADT was not reported.

The effect of rye bran bread (295 gm daily), a rich source of phytoestrogens, was examined in a 3-week trial in 18 men with untreated prostate cancer. There was no change in PSA between the intervention and control groups (wheat), and PSADT was not reported.

**Plant based diet.** In the Men's Eating and Living study the effect of a 6-month telephone based counseling intervention on dietary behavior change was evaluated using a plant based diet that was rich in vegetables, including 2 servings of tomatoes. PSA was a secondary end point, and did not differ between the diet intervention group (42 men on active surveillance or after primary treatment (10)) and matched historical controls (25).

### Table 2. Nonrandomized, uncontrolled diet and/or dietary supplement trials

<table>
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<tr>
<th>References</th>
<th>Intervention</th>
<th>Subjects</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Jatoi et al</td>
<td>Green tea (6 gm)</td>
<td>Men with prostate Ca with elevated PSA with androgen independent disease (42)</td>
<td>1–5 Mos</td>
</tr>
<tr>
<td>Demark-Wahnefried et al</td>
<td>Low fat diet (20% total calories), flaxseed (30 gm)</td>
<td>Men with prostate Ca awaiting prostatectomy (25) and matched historical controls (25)</td>
<td>21–77 Days (mean 34)</td>
</tr>
<tr>
<td>Nguyen et al</td>
<td>Plant based diet and stress reduction</td>
<td>Men with prostate Ca with increasing PSA after primary treatment (13)</td>
<td>6 Mos</td>
</tr>
<tr>
<td>Saxe et al</td>
<td>Plant based diet and stress reduction</td>
<td>Men with prostate Ca with increasing PSA after prostatectomy (10)</td>
<td>4 Mos</td>
</tr>
<tr>
<td>Cipolla et al</td>
<td>Phytoestrogens reduced diet (concurrent neomycin chemotherapy)</td>
<td>Men with metastatic HRPC (13)</td>
<td>2–26 Mos (mean 8)</td>
</tr>
<tr>
<td>Pantuck et al</td>
<td>Pomegranate juice (250 ml)</td>
<td>Men with recurrent prostate Ca with increasing PSA after primary treatment (46)</td>
<td>6–40 Mos (until disease progression)</td>
</tr>
<tr>
<td>Chen et al</td>
<td>Tomato sauce rich diet (30 mg lycopene)</td>
<td>Men with prostate Ca awaiting prostatectomy (32)</td>
<td>3 Wks</td>
</tr>
<tr>
<td>Jatoi et al</td>
<td>Meatless spaghetti sauce or juice (30 mg lycopene)</td>
<td>Men with asymptomatic androgen independent prostate Ca with increasing PSA (46)</td>
<td>1–10 Mos (mean 3)</td>
</tr>
<tr>
<td>Spentzos et al</td>
<td>Step 1: Low fat diet (15%), vitamin E (400 IU), selenium (200 mcg), multivitamins</td>
<td>Men with prostate Ca with increasing PSA after primary treatment (15)</td>
<td>Median 3.9 mos (step 1), 5.4 mos (step 2)</td>
</tr>
<tr>
<td>Aronson et al</td>
<td>Step 2: Addition of soy isolavones (114 mg) + soy protein (33.5 gm)</td>
<td>Men with prostate Ca with increasing PSA (14), either early (7) or metastatic disease (7)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Thomas et al</td>
<td>Low saturated fat diet rich in fruits and vegetables, sodium salicylate (350 mg), manganese gluconate (20 mg), copper gluconate (20 mg), vitamin C (400 mg), multiple vitamin and mineral supplement†</td>
<td>Men with prostate Ca with increasing PSA after various treatments or observation</td>
<td>6 Mos</td>
</tr>
<tr>
<td>Durak et al</td>
<td>Garlic extract (1 ml/kg)</td>
<td>Men with prostate Ca with increasing PSA after primary treatment (10)</td>
<td>12 Mos</td>
</tr>
<tr>
<td>Guest et al</td>
<td>Citrus pectin (800 mg)</td>
<td>Men with prostate Ca with increasing PSA after primary treatment (10)</td>
<td>Variable until disease progression</td>
</tr>
<tr>
<td>Choo et al</td>
<td>Green tea extract (500 mg)</td>
<td>Men with prostate Ca with increasing PSA after primary treatment (10)</td>
<td>12 Mos</td>
</tr>
<tr>
<td>Ansari and Gupta</td>
<td>Lycopene (10 mg)</td>
<td>Men with metastatic HRPC with increasing PSA (20)</td>
<td>3 Mos</td>
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<tr>
<td>Clark et al</td>
<td>Lycopene (15, 30, 45, 60, 90, 120 mg)</td>
<td>Men with prostate Ca with biochemical relapse after local therapy (36)</td>
<td>12 Mos</td>
</tr>
<tr>
<td>Lissone et al</td>
<td>Melatonin (20 mg), triptorelin (LHRH analogue)</td>
<td>Men with metastatic HRPC (14), progressing on triptorelin, with poor prognosis</td>
<td>Variable until disease progression</td>
</tr>
<tr>
<td>Hussain et al</td>
<td>Phytoestrogens: soy isoflavones (200 mg)</td>
<td>Men with prostate Ca with increasing PSA (39); heterogeneous group</td>
<td>0.8–6 Mos (median 5.5)</td>
</tr>
<tr>
<td>deVere White et al</td>
<td>Phytoestrogens: soy isoflavones (900 mg)</td>
<td>Men with prostate Ca with increasing PSA (52); after various treatments or observation</td>
<td>6 Mos</td>
</tr>
<tr>
<td>Vaishampayan et al</td>
<td>Phytoestrogens: soy isoflavones (80 mg), lycopene (30 mg)</td>
<td>Men with prostate Ca with increasing PSA (71); lycopene (38), lycopene and isoflavones (33)</td>
<td>Median 6 mos lycopene, 5.5 mos lycopene plus soy isoflavones</td>
</tr>
<tr>
<td>Jarred et al</td>
<td>Phytoestrogens: red clover (160 mg)</td>
<td>Men with prostate Ca awaiting prostatectomy (18) and historical matched controls (18)</td>
<td>7–54 Mos (median 20)</td>
</tr>
<tr>
<td>deVere White et al</td>
<td>Shiitake mushroom extract (8 gm)</td>
<td>Men with localized or metastatic prostate Ca with elevated PSA (61)</td>
<td>6 Mos</td>
</tr>
<tr>
<td>Flagg et al</td>
<td>Silybin phytosome (2.5–20.0 gm)</td>
<td>Men with prostate Ca with increasing PSA (19)</td>
<td>12–52 Wks (median 24)</td>
</tr>
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</table>

* Nonrandomized, uncontrolled clinical trial (part of a larger placebo controlled clinical trial).
† Dosages based on <50 kg body weight. For men >50 kg the dose was doubled.
agents including soy isoflavones (table 1).20 Positive outcomes for lycopene supplementation either alone or in combination with other agents were reported in 2 of these studies.20,21 Ansari and Gupta reported a statistically significant difference in PSA between the lycopene (4 mg) and orchietomy treated group and control group of men with metastatic disease who underwent orchietomy, based on values of 9.02 ± 7.5 and 3.01 ± 1.9 ng/ml (p = 0.001).23 It is unclear if the analysis represents a comparison of the difference in mean change in PSA between groups or is a before and after analysis. PSADT was not reported in this study.

Schroder et al reported a significant increase in free PSADT (1,150 vs 445 days) in the per protocol group compared to controls (p = 0.041).20 This was a crossover study of 15 mg lycopene and multiple other compounds in men treated for 10 weeks with a 4-week washout period (24-week study). In the second treated group (intent to treat) there was a nonsignificant trend in PSADT increase (p = 0.089) and no difference in total or free PSA. In the remaining study no statistically significant benefits on PSA from lycopene supplementation were reported.19 It should be noted that 2 additional studies evaluated lycopene within a fortified margarine18 or as tomatoes (2 servings within a plant based diet).22,23

**Phytoestrogens.** In addition to 5 dietary trials of phytoestrogen rich diets, were 2 studies on soy isoflavones.18,20 These RCTs evaluated soy isoflavone supplements (100 mg or less) in men with increasing PSA18,20 and both included concurrent use of other agents such as lycopene, vitamin E, selenium or green tea. In the crossover study there was an increase in free PSADT in the first treatment group compared to controls after 10 weeks.20 In the other study there was no significant increase in total PSADT (41 vs 44 weeks, p = 0.84) and a significant decrease in free PSA (68 weeks vs a half-life of 13 weeks, p = 0.02).18

Toxicity attributed to the various interventions was reported in 6 of 9 trials and there were no serious adverse effects.15,17–20,24 Mild gastrointestinal intolerance was associated with 2 separate dietary interventions including soy and rye bran,16,17 and 2 dietary supplement trials using multiple agents.16,20 The number of men either excluded from or who dropped out of the study ranged from 0%21 to 7% to 22%.16–18,24 Various measures of compliance included self-reported intake/diet records and/or objective biomarkers.

**NONRANDOMIZED UNCONTROLLED TRIALS**

The remaining 23 trials were nonrandomized and uncontrolled. Therefore, the study characteristics only are summarized in table 2 without outcome data or conclusions of investigators. In these studies the respective interventions were largely evaluated in a before and after analysis of data from individual patients or group means. There was no control group in any of these studies except in a low fat diet trial (supplemented with flaxseed) of age matched controls.25 All other studies used pretreatment PSA values from the same study participants as a comparison. In several studies the primary analysis included descriptive statistics to calculate the number (frequency) of men with PSA responses, generally within 1 or more of the 4 main categories of complete response, partial response, stable disease and disease progression.21,27–40

**DISCUSSION**

The potential for diet and dietary supplements to alter disease progression or recurrence in men with prostate cancer has led to the design of numerous intervention studies. However, no reviews to date represent a comprehensive evaluation of evidence from recent intervention trials conducted in men with established prostate cancer. Only 1 review included a significant number of RCTs, which included less than half (44%) of those identified in this review.10 Therefore, our review is uniquely positioned, with emphasis on trials with an RCT design.

Dietary and lifestyle interventions are of particular interest in prostate cancer because of the often long disease latency. Many believe there may be opportunity to prevent disease progression and recurrence, and/or alleviate comorbidities and treatment associated symptoms during the waiting periods after diagnosis and/or primary treatment. Nontoxic dietary and/or naturally derived interventions may have the potential to slow disease progression and/or improve quality of life. As a consequence, the interest in and investigation of diet and dietary supplements to delay the progression of prostate cancer and the considerable morbidity associated with conventional treatments are increasing. Approximately three-quarters of the studies in this review were published within the last 5 years and several United States National Institutes of Health funded trials are currently in progress (http://www.clinicaltrials.gov).

Evaluation of various diet and dietary supplement interventions in men with prostate cancer has relied largely on PSA as a biomarker of disease progression. The PSA serum test has gained widespread acceptance by medical professionals and is heralded as the most predictive serum test when used as part of a screening protocol for diagnosing prostate disease. While there is active debate regarding its accuracy when used alone to predict prostate cancer incidence and progression, more than 200 studies have used PSADT as a surrogate end point for prostate cancer progression in the design of clinical trials.41 Discrepancies are known to exist between PSADT values determined for identical data sets depending on the method used for calculation. The log slope method, which incorporates multiple successive measurements of PSA in the calculation, is superior to the 2 point method, which ideally would only be applied when data sets are limiting. Regardless, both methods produce a PSADT which is predictive of disease progression.

This review of 32 studies gives priority to evidence from 9 RCTs that used PSA and/or PSADT as end points (table 1). Overall, when examining the strongest evidence it appears that diet and dietary supplement interventions can alter surrogate biomarkers for prostate cancer progression. In 3 of 7 studies in which PSA was reported as the end point there was a significant decrease in the intervention group compared to controls using soy, lycopene supplements (assuming a control group comparison) and a low fat vegan diet as part of a comprehensive lifestyle program.16,21,24 In contrast, the remaining studies on PSA revealed no statistically significant difference in PSA.15,17–20,22,23 PSADT was less frequently included as an end point. Of the 2 studies in which PSADT was reported 1 demonstrated a significant 2.6-fold increase (p = 0.041) using multiple dietary supplements20 and no difference was reported in the other (p = 0.84).18
In summary, the results are mixed in that trials including lycopene supplements and/or phytoestrogens do not always show a benefit. Ansari et al reported positive findings for a low dose (4 mg) of lycopene supplements in men with metastatic disease who underwent orchiectomy, although the trial design did not allow assessment of lycopene alone (without orchiectomy). In comparison, a 30 mg dose of lycopene in men awaiting prostatectomy showed no benefit. In the case of the phytoestrogens the food source varied from soy (grits, protein and tofu) to rye bran or an isoflavone supplement (62.5 and 100 mg) and was often combined with other agents. Of the 4 RCTs with positive findings a combination of 1 or more diet and/or dietary supplement interventions was used in 2, suggesting that comprehensive diets or combined agents may be more beneficial in preventing cancer progression. It is plausible that there are potential additive or synergistic effects of compounds that result in clinically meaningful benefits. Only 1 RCT conducted in men with metastatic HRPC measured survival and did not appear to have been specifically designed or powered to evaluate this end point, thus no conclusions can be drawn. In the RCT by Ornish et al other potential benefits included improved quality of life and weight loss, suggesting a potentially important role of diet in men with prostate cancer.

The potential benefits of the diet and dietary supplement intervention studies in delaying prostate cancer progression, albeit modest, are viewed more positively due to the lack of serious adverse effects. While there was limited if any toxicity related to the diet and dietary supplement interventions in the trials examined, adverse effects can occur and patients with cancer need to be aware that any intervention whether dietary or supplement based, even if natural, may have adverse effects. In addition, concerns have been raised about the lack of regulation of supplements and potential interactions with treatment.

In the studies reviewed compliance was generally rated highly, as assessed by a combination of self-report and objective measures. When used, serum and urinary biomarkers demonstrated good adherence to the study agent and their use is encouraged in future trials to increase confidence in the adherence to the intervention and absence of contamination in controls.

It is not possible to draw meaningful conclusions from the majority of the remaining studies, as they were nonrandomized and uncontrolled (Table 2). In the absence of a comparison group in these trials interpretation of the data is difficult. Regardless, diet and dietary supplement studies that are less rigorous in design and past review articles discussing them have unfortunately been widely quoted as evidence of the efficacy of these interventions, as a benefit or lack thereof. This has potential disadvantages and can also jeopardize further research.

The main limitations identified in this review were that few studies used a rigorous RCT design and improvements in PSA or PSADT as primary end points may not necessarily be associated with a decrease in disease progression or recurrence. In addition, although PSADT (log slope method) is a stronger indication of progression than PSA it was only reported in 2 studies. Other limitations were that most studies had a small sample size and were of short duration. Furthermore, many studies tested multiple interventions with variations in dose and composition of interventions, and diverse patient populations, making direct comparison of the RCTs difficult. In addition, significant weight loss was noted in 1 dietary intervention study as a confounding factor.

The trials identified in this review were important early studies evaluating novel and innovative strategies to prevent or delay prostate cancer progression and potentially limit patient exposure to treatment morbidity. Additional research on dietary and dietary supplement interventions is warranted and several recommendations are made for future studies. Randomized controlled trials designed with adequate statistical power are needed and this appears to be addressed in several National Institutes of Health funded studies in progress. In addition, the use of study designs that correlate changes in surrogate biomarkers with tumor volume or prostate biopsy are needed, as well as inclusion of men with early disease and advanced disease, longer intervention periods and/or extended followup to allow for the measurement of cancer recurrence and survival. The latter would allow for stratification of samples and control for known confounding prognostic factors (medical as well as others such as obesity) that are associated with prostate cancer progression and survival. Increased body mass appears to have a more consistent association with prostate cancer mortality than incidence, and recent studies suggest that it may be related to higher recurrence rates after prostatectomy and radiation therapy. Therefore, interventions that stratify for this variable or are designed to reduce body weight are likely to provide useful information and possible benefits. Future investigators are recommended to include a more detailed description of trial participants such as height, weight, BMI and race in the event that there are differential findings within specific patient populations.

Diet and dietary supplement interventions require lifestyle modifications that may be challenging. However, these interventions are often regarded favorably by patients if presented as a nontoxic alternative to cancer treatment or to delay treatment. Men with prostate cancer participating in a trial of complementary and alternative medications had positive but realistic expectations and they enrolled in the trial largely because it was perceived as natural with fewer side effects. In clinical experience patients also express that diet and dietary supplements help to regain a sense of control and address feelings of anxiety during active surveillance or increasing PSA. In terms of patient enrollment and adherence there may also be benefits in enrolling men with limited clinical options (eg men under active surveillance or those with recurrent disease) as they may be highly motivated to participate and participation may have added psychosocial impacts in assisting them with coping with the disease. Lastly, further research is needed to identify target patient populations, and the most effective types and intensity of diet and dietary supplement interventions to promote sustainable behavior change, particularly in longer trials.

CONCLUSIONS
A limited number of RCTs were identified in which dietary and dietary supplement interventions appear to slow disease progression in men with prostate cancer, although results vary. Studies were limited by reliance on the surrogate biomarker PSA as well as sample size and study duration. Well designed trials to expand knowledge and replicate find-
ings are warranted to assess the impact of dietary and dietary supplement interventions on preventing and reducing recurrence and morbidities associated with treatment.

ACKNOWLEDGMENTS

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Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>HRPC</td>
<td>hormone refractory prostate cancer</td>
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<tr>
<td>PSA</td>
<td>prostate specific antigen</td>
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<tr>
<td>PSADT</td>
<td>prostate specific antigen doubling time</td>
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<tr>
<td>RCT</td>
<td>randomized, controlled trial</td>
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41. Daskivich TJ, Regan MM and Oh WK: Prostate specific antigen doubling time calculation: not as easy as 1, 2, 4. J Urol 2006; 176: 1927.


EDITORIAL COMMENTS

The field of complementary and alternative medicines, and their use in treating cancer can be difficult and confusing, especially for the general practicing physician. There is a seemingly endless array of epidemiological and laboratory studies in cell lines and animal studies that indicate dietary changes and supplements may be useful in treating a host of different cancers, including prostate cancer. In addition, the manufacturers of various natural supplements make broad statements about the efficacy of their products that may or may not have been rigorously tested. As a consequence, it is often difficult and confusing for patients and doctors to filter out the facts from the noise. This is just as true for prostate cancer as it is for other cancer types. This review highlights those studies that have attempted to test various diets and dietary supplements using the most rigorous testing method, RCTs.

The ultimate conclusion is sobering and encouraging. On the one hand, the number of trials that met the study criteria was disappointingly small and the trials often were small, of relatively short duration and in all but 1 case used a surrogate end point for the outcome of serum PSA. As a consequence, this review appropriately cautions us that definitive proof that these complementary and alternative medicines are effective in the management of prostate cancer is still lacking. On the other hand, the evidence is sufficiently compelling that larger scale, well designed trials are clearly warranted. It is also apparent that patients are interested and motivated to participate in complementary and alternative medicine related trials, especially for prostate cancer. Therefore, the onus is on the research community to design, implement and complete these trials so that physicians and patients can make more rational, evidence-based choices about the use of diet and supplement based therapies for prostate cancer.

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A decrease in PSA was reported for some interventions including low fat vegan diet, soy beverage and lycopene, a constituent of tomatoes. This is important information. Patients are being bombarded with information from questionable sources. For instance, if patients google “prostate cancer alternative medicine,” they obtain about 280,000 hits (July 2008). Much of that information is unreliable to say the least.1

Doctors must be aware of the evidence and communicate with their patients effectively. A full medical history should include questions on supplements and other alternative treatments. Furthermore, we should be concerned about the
plethora of misinformation. Currently the shelves of our bookshops are stacked with literature which is woefully inadequate. Newspaper reports are equally unreliable. Therefore, Singh and I have recently grasped the nettle and published a critical analysis for lay people. This brought us plenty of hate mail and insults from the supplement industry but if it also contributed to a more balanced view, the effort must have been worth it.

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The use of complementary and alternative medications continues to increase at the same time that 1) their production and sale remains outside the regulation of the Food and Drug Administration, and 2) critical investigation regarding their use remains hindered by the duration and expense of these trials, uncertainty regarding the prevalence of prostate cancer in controls and difficulties with end points such as end of study prostate biopsies vs prostate biopsies for cause in the PCPT (Prostate Cancer Prevention Trial). Thus, the increased use of complementary and alternative medications remains hindered by a lack of scientific data from randomized clinical trials to justify their use, as so ably demonstrated in this review. In addition, patients, pharmacists and treating physicians must remain vigilant about interactions that occur among these medications as well as between these and prescription medications. This responsibility is made more difficult because most patients do not consider complementary and alternative medicines to be medications that they should report to their health care providers. The most recent increase in public enthusiasm for what might be considered complementary and alternative medicine is the use of vitamin D. Fortunately many carefully performed intervention and chemoprevention studies are currently under way to assess the value of vitamin D therapy for prostate cancer.

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