Minimal Effect of a Low-Fat/High Soy Diet for Asymptomatic, Hormonally Naive Prostate Cancer Patients

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ABSTRACT

Purpose: The effects of a low-fat diet or a low-fat diet with the addition of a soy supplement were investigated in a pilot Phase II study for asymptomatic, hormonally naive prostate cancer patients with rising prostate-specific antigen (PSA) levels.

Experimental Design: A two-step intervention was implemented. During step 1, patients were begun on a low-fat diet with a goal to reduce fat intake to 15% of total daily calories. On PSA progression, a soy protein supplement was added to the diet (step 2). The primary end point was PSA reduction by 50%. Secondary end points were PSA doubling time and time to progression (TTP). Serum was analyzed for changes in the sex hormone and insulin-like growth factor (IGF-I) axes.

Results: Among 18 evaluable patients, (median follow-up on study 10.5 months), no patient on either step had a PSA reduction by 50% at any time. There was a trend toward a longer PSA doubling time (P = 0.06) and a prolongation in estimated median TTP of ∼3 months (P = 0.018) during step 2 compared with step 1 of the study. During step 1, free testosterone levels decreased by 5% (P < 0.01), and during step 2, IGF-I levels increased by 22% (P = 0.02).

Conclusions: A low-fat diet with the subsequent addition of a soy supplement did not result in a significant decline in PSA levels. The addition of soy protein had a modest effect on TTP. A potentially undesirable effect associated with the administration of soy was an increase in IGF-I serum levels.

INTRODUCTION

A variety of alternative therapies are increasingly being used for the treatment of prostate cancer. In particular, there is great interest in the role of diet and dietary supplements. Interest in the therapeutic potential of dietary modification has been sparked by epidemiological data supporting an association between certain diets and prostate cancer risk (1–3). For instance, the lower fat and high soy diet of Asian men has been proposed as a major reason why men from these countries have a decreased incidence and death rate from prostate cancer (1).

Despite evidence supporting the effect of diet and dietary supplements on prostate cancer prevention, the value of dietary management for patients who have already developed the disease has not been investigated rigorously. However, because low-grade asymptomatic prostate cancer is relatively ubiquitous in autopsy series of aging men (4), it is possible that dietary interventions may delay the progression of minimal tumor burden prostate cancer.

For these reasons we decided to perform a pilot study focusing on the role of a low-fat diet and soy supplementation for the management of asymptomatic patients with rising PSA values after definitive local therapy. These patients (commonly referred to as having stage “D0” prostate cancer) will typically not develop overt metastases for several years (5, 6), and their optimal management has still not been defined (7).

A sequential, two-step dietary intervention scheme was implemented in this pilot study. During step 1, patients were given selenium, vitamin E, and multivitamins, and instructed by the study dietician on how to institute and follow a low-fat diet with the goal that 15% of total calories be derived from fat. At the time of PSA progression, patients were begun on step 2 of the intervention. While maintaining their low-fat diet and vitamin supplements, they were supplied with a soy supplement. The target that ≤15% of total calories be derived from fat was based on the approximate fat content of the Asian diet (1), and the dose of soy we used has been used in previous dietary studies (8–11). We also sought to standardize vitamin and mineral intake by providing a multivitamin, and vitamin E and selenium at doses used in the ongoing national prevention trial (12–14). The two-step design offered a mechanism for reliably assessing PSA progression rates between steps in the trial, and the opportunity to determine whether the addition of soy to a

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The abbreviations used are: PSA, prostate-specific antigen; PSAdT, prostate-specific antigen doubling time; TTP, time to progression; IQR, interquartile range; P, insulin-like growth factor; IGFBP-3, insulin-like growth factor binding protein-3; CI, confidence interval.
low-fat diet resulted in additional benefit compared with a low-fat diet alone.

The primary end point in this study was PSA reduction by 50%. Secondary end points were alteration in PSAdT and time to PSA or clinical progression (TPP). We also assessed alterations in androgen and IGF-I axes, two pathways known to affect prostate cancer progression (15–17) and to be influenced by fat reduction and soy intake (18–20). We hypothesized that both fat reduction and soy supplementation might have additive effects on decreasing the levels of these hormones.

MATERIALS AND METHODS

Inclusion Criteria. The study population consisted of patients who had undergone primary therapy (radiation or surgery) for biopsy-proven adenocarcinoma of the prostate. Patients also had to exhibit rising PSA values (two consecutive values taken at least 1 week apart) above the postprostatectomy nadir value with the second higher than the first. Eligible patients also had to have a PSA value of at least 0.5 ng/ml if they had been treated with prostatectomy, or a PSA value of at least 1.0 ng/ml if they had been treated with radiation therapy.

Exclusion Criteria. Patients meeting the following criteria were ineligible for the study: (a) need for treatment with any conventional modality (surgery, radiation therapy, and hormonal therapy); (b) prior treatment with hormonal therapy unless it was given in a neoadjuvant or adjuvant setting and >1 year before entry; (c) symptoms related to prostate cancer; (d) evidence of metastatic disease on imaging studies; (e) history or evidence of overt renal, hepatic, or bone marrow failure; (f) requirement for insulin or coumadin therapy; and (g) history of a prior or concurrent malignancy other than nonmelanoma skin cancer. Patients using concurrent therapy for prostate cancer, including PC-SPES, other herbal products, or finasteride, or already taking supplemental soy or on a low-fat diet were also excluded. However, patients taking multivitamins with or without additional selenium and/or vitamin E were eligible for this study. The protocol was approved by the Institutional Review Board at the Beth Israel Deaconess Medical Center, and written informed consent was required of all of the patients to enter the study.

Study Procedures. After enrollment, patients underwent a baseline evaluation in which they received dietary instructions, and their dietary habits were assessed by one of the study nutritionists (H. M., S. G.). Patients and their spouses were required to meet with one of the nutritionists every other month for the duration of the study to analyze their diet and food records, and to receive feedback. The goal of the dietary instruction was to restrict dietary fat intake to 15% of total daily caloric calories from either saturated or unsaturated sources of dietary fat. In addition, study patients were given 2-month supplies of vitamin E (400 IU/day; CVS, Woonsocket, RI), selenium tablets (200 µg/day; CVS), and multivitamins (Spectravite; CVS). The low-fat dietary instruction constituted step 1 of the intervention.

PSA progression (see "End Points" section below) triggered step 2 of the intervention, in which a soy protein supplement (Take-Care; Nutrious Foods, Inc., St. Louis, MO) was added to the regimen. The soy packets were to be mixed with juice or water and taken twice per day. Each serving (packet) contains 57 mg of isoflavone and 3.4 mg/isoflavone/g soy protein. The isoflavone in this product consists of 2.1 mg genistein, 1.1-mg diadzein, and 0.2 mg glycitsen/g of soy protein. Patients on step 2 continued to follow the low-fat diet and to meet every other month with a nutritionist.

Compliance to the low-fat diet was monitored through food records. Patients were asked to complete three food records every month (two random weekdays and one random weekend day) in which intake of all of the foods were recorded. The food records were analyzed by NDS-R Version 4.03, Nutrition Data System for Research. Compliance for soy, vitamin E, selenium, and multivitamin intake was monitored by counting the number of unused pills or powder packets returned at nutritionist visits.

Compliance to the low-fat component of the diet was assessed by determining how many patients were able to decrease dietary fat to <15% of total calories.

Patients underwent monthly PSA tests, and every other month physician visits with physical examination and interval history. Imaging studies were performed on a symptom-directed basis. Patients were designated as reaching an end point and withdrawn from the study if documented clinical progression or PSA progression during step 2.

Hormonal assays (testosterone, estradiol, IGF-I, and IGFBP-3) were performed from serum obtained at entry, after 2 months on step 1, at the initiation of step 2, and after 2 months on step 2. Specimens were always collected from fasting patients between 9 a.m. and 11 a.m., and maintained at –80°C until assayed. Hormonal assays were performed using commercially available immunoradiometric assays. The estradiol assay (DPC, Los Angeles, CA) has a sensitivity of 0.8 pg/dl and a 5.3% and 6.4% intra- and interassay coefficient of variation. Total testosterone (DPC) has a sensitivity of 4 ng/dl and an intra- and interassay coefficient of variation of 5.3%, and free testosterone (DPC) has a sensitivity of 0.15 pg/ml and 11.6% precision. IGF-I (Diagnostic System Laboratories, Webster, TX) has a sensitivity of 2.06 ng/ml and intra- and interassay coefficient of variation of 4.9 and 5.1%, respectively. IGFBP-3 (Diagnostic System Laboratories) has a sensitivity of 0.5 ng/ml, and an intra- and interassay coefficient of variation of 3%.

End Points. Patients had to remain on study for at least 2 months to be considered evaluable. The primary study outcome was PSA decline of at least 50% from baseline value confirmed by a repeat test 1 month later. The study was designed based on the Gehan model (21) to detect a 20% response rate among D0 patients. The initial sample size was 14 evaluable patients; if no patient demonstrated a 50% PSA decline, then no additional patients would be enrolled, and the interventions would be judged to be ineffective. Conversely, if 1, 2, 3, or 4 responses were observed among the first 14 evaluable patients, then an additional 1, 6, 9, or 11 patients, respectively, would be enrolled. With this design, if the response rate is 20%, then the probability of observing no responses in 14 patients and incorrectly judging the intervention as ineffective is <5%. Enrollment continued to 19 patients, because we anticipated that ~15% of patients on each step would be evaluable. Furthermore, responses for the primary end point could not be assessed until step 2 was completed and enrollment was continued during...
The median time on entire study (step 1 and step 2) was 10.5 months (range, 3–45 months), and the median number of PSA values obtained was 13 (range, 4–46 values). Three patients continuing on study have been followed for 19, 25, and 45 months. During step 1, there was a median of 6 PSA measurements collected over a median follow-up time of 3.9 months. For the 17 patients who entered phase 2 of the study, there was a median of 6 PSA measurements collected over 5.4 months (Table 2).

**Toxicity.** The dietary regimen was well tolerated, and there were no serious adverse events related to these therapies. One patient had a feeling of fullness that he ascribed to soy intake, but this resolved spontaneously even while he continued on the soy supplement.

**Compliance and Weight Changes.** Food records were obtained from 16 of 18 evaluable patients. Food records were analyzed for percentage of calories from carbohydrates, fat, and protein during step 1 of the study. (Table 3). Percentage of calories from fat were calculated for an average of 4 days for the baseline period and 8 days for during the first 6 months on the study. Only 2 of 16 patients averaged <15% of calories during step 1. The average percentage of calories from fat was 36% at baseline (before entry) and 19% during the first 6 months of the trial (and 23% for the first 2 months of the study and 20% for the 2 months before transition to soy, Table 2). On average, patients decreased their total calories from fat sources by 17%. Compliance with the soy powder, vitamin E, selenium, and multivitamins was excellent.

Although patients were instructed to maintain pretreatment levels of calorie intake, there was a median weight loss of 5 pounds (IQR: –8 to 0 lbs; P < 0.01) during step 1 of the study. This occurred in most patients during the first 2 months of step 1. There were no significant changes in weight during the remainder of the study.

**Clinical End Points.** None of the 18 evaluable patients had a decline from baseline PSA by ≥50% at any time during their participation in the study, neither on step 1 or step 2.

Among the 18 evaluable patients, 17 progressed on step 1 and continued onto step 2. One patient moved out of the area and withdrew before progression. The median estimated PSAdT was 7.6 months (IQR: 5.3–13.8 months; Table 2); the longest estimated PSAdT is >3 years in a patient who continues on study. The median estimated TTP is 3.4 months (95% CI, 3.0–9.7 months; Table 2).

For the 17 patients who continued onto step 2 of the intervention, 8 demonstrated PSA progression, 2 demonstrated clinical progression, 4 withdrew, and 3 patients continue on the study. Three of the patients who withdrew from the study during step 2 were beginning to demonstrate PSA progression and chose to discontinue the study. Another patient withdrew because of comorbid illness unrelated to his disease or the study. For step 2, the median estimated PSAdT was 11.3 months (IQR: 6.7–39.5 months; Table 2). Ten of 17 (59%) subjects who progressed on step 1 and continued onto step 2 have a longer PSAdT on step 2. No patient had a shorter PSAdT on step 2 than on step 1. For each patient, the difference in PSAdT between step 1 and step 2 was calculated by a paired analysis. The median prolongation in PSAdT is 5 months on step 2 compared with step 1 (P = 0.06 by Wilcoxon signed rank test; Table 2).

### Table 1. Characteristics of patients at study entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [median (range)]</td>
<td>71 (59, 81)</td>
</tr>
<tr>
<td>PSA (ng/ml) [median (IQR)]</td>
<td>11.0 (6.1, 15.0)</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group performance status of 0</td>
<td>100%</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>African American (n)</td>
<td>4</td>
</tr>
<tr>
<td>Caucasians (n)</td>
<td>14</td>
</tr>
<tr>
<td>Primary therapy*</td>
<td>6</td>
</tr>
<tr>
<td>Prostatectomy (n)</td>
<td>14</td>
</tr>
</tbody>
</table>

*Two patients had both radical prostatectomy and subsequently radiation therapy as primary or adjuvant treatment. Eastern Cooperative Oncology Group performance status of 0 denotes patients with no decline in activities of daily living.

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Table 2 Summary of patient follow-up and clinical outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Step 1 low-fat</th>
<th>Step 2 low-fat/high-soy</th>
<th>Difference or hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>18</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Number of PSA measurements [median (IQR)]</td>
<td>6 (5, 10)</td>
<td>6 (5, 10)</td>
<td>—</td>
</tr>
<tr>
<td>Length of follow-up (months) [median (IQR)]</td>
<td>3.9 (3.0, 7.1)</td>
<td>5.4 (3.0, 7.2)</td>
<td>—</td>
</tr>
<tr>
<td>PSAAdT (months; median (IQR))</td>
<td>7.6 (5.3, 13.8)</td>
<td>11.3 (6.7, 39.5)</td>
<td>5.0 (–1.1, 20.9)</td>
</tr>
<tr>
<td>Time to progression (months) [median (95% CI)]</td>
<td>3.4 (3.0, 9.7)</td>
<td>6.3 (4.4, ∞)</td>
<td>0.29 (0.11, 0.81)</td>
</tr>
</tbody>
</table>

* IQR denotes interquartile range [25th, 75th percentiles]; progression is PSA or clinical progression.

* Difference in PSAAdT (Step 2–Step 1), $P = 0.06$ by Wilcoxon signed rank test; or hazard of progression (Step 2 relative to Step 1), $P = 0.018$ by proportional hazards model.

Table 3 Average percentage of calorie intake from carbohydrates, protein, and fat

<table>
<thead>
<tr>
<th>Total calories CHO Protein Fat</th>
<th>Baseline (n = 16)</th>
<th>Month 2 (n = 16)</th>
<th>Soy baseline (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1644 Kcal</td>
<td>47%</td>
<td>16%</td>
<td>36%</td>
</tr>
<tr>
<td>1381 Kcal</td>
<td>59%</td>
<td>18%</td>
<td>23%</td>
</tr>
<tr>
<td>1569 Kcal</td>
<td>60%</td>
<td>20%</td>
<td>20%</td>
</tr>
</tbody>
</table>

* $n$: the number of patients who have food records available for analysis.

The median TTP was 6.3 months on step 2, which is ~3 months longer than on step 1. The hazard of progression on step 2 was ~30% of that on step 1 (significant at $P = 0.018$ by proportional hazards model).

**Hormonal End Points.** Baseline and 2-month serum samples were analyzed for 18 of 18 (100%) and 17 of 18 (94%) patients, respectively, during step 1 of the dietary intervention (Table 4). After adjusting for weight changes there was a statistically significant decrease in free testosterone (median, −5%; $P < 0.01$). IGF-I and IGFBP-3 levels were adjusted for weight changes and for each other, because lower levels of IGFBP-3 result in higher levels of bioavailable IGF-1 (15). There was a median increase in IGF-1 levels of 9% ($P = 0.09$) and a median decrease in IGFBP-3 of 10% ($P = 0.02$). There were no significant changes in total testosterone or estradiol over the first 2 months of step 1 (Table 4).

Of the 17 D0 patients who continued onto step 2 of the intervention, baseline and 2-month serum were available for 16 (93%) and 15 (88%) patients, respectively. During step 2 of the intervention, there was a significant increase in IGF-I levels ($P = 0.02$ adjusted for changes in weight and IGFBP-3) but no change in IGFBP-3 levels. There was a trend toward a decline in total testosterone ($P = 0.06$ adjusted for weight change).

When hormone levels were assessed from the initiation of the study through month 2 on soy, IGF-I levels increased cumulatively by a median of 35% ($P < 0.01$) with no corresponding change in IGFBP-3 levels. In contrast, during the same time interval there were statistically significant decreases in both free (17%) and total testosterone (15%; each $P < 0.05$).

**DISCUSSION**

The primary end point of this study was to determine whether dietary intervention, either in the form of a low-fat diet with vitamin E and selenium, or the same diet combined with soy, resulted in PSA declines of ≥50% in patients with stage D0 prostate cancer. No patient in this study achieved this level of PSA decline. The 50% decline in PSA values from entry was chosen as an end point because it has been associated with a survival advantage, at least for patients with hormone-refractory disease (22).

Although significant declines in PSA were not achieved by this type of intervention, the secondary end points of change in PSAAdT and TTP are important to analyze. This is because patients with longer PSAAdTs have been shown to have an increased TTP to overt metastatic disease (5). Although hormonal therapy may result in a survival benefit for D0 patients (23), this has not been demonstrated with certainty (24), and this therapy is associated with significant side effects. Therefore, if a dietary intervention could significantly slow PSA progression, it may be of clinical benefit.

The low fat diet in combination with selenium and vitamin E instituted during step 1 of this study was unlikely to have had an effect on PSAAdT or TTP. In fact, during step 1 of the intervention, PSAAdTs were actually shorter by at least 2.5 months than the median values observed in series of D0 patients after either radiation therapy (median, 12 months) or surgery (median, 10 months; Refs. 5, 6).

Although it is not possible to compare step 1 values for PSAAdT and TTP to pre-enrollment values, the PSAAdT and TTP measured during this phase of the study did serve as a suitable and accurate comparator to the corresponding values obtained during step 2. During this phase, with the addition of soy to the dietary regimen, there was a trend toward a prolongation in PSAAdT and a significant prolongation in TTP. In fact, more than half of the patients in this study demonstrated a slower PSAAdT and a longer TTP during step 2 (data not shown). Furthermore, this apparent delay was observed in patients after they had already progressed on step 1, and might have been less likely to achieve a response as they may have entered a more aggressive phase of their illness.

The trend toward a delay in PSA progression and significant prolongation in TTP during step 2 suggests that the addition of soy has some inhibitory effects on prostate cancer progression. However, it is not possible to conclude this with certainty. We interpret the analysis comparing TTP between dietary steps with caution. If the 3 patients that had rising PSAs and withdrew during step 2 before reaching a defined end point are assessed as progressors, the median TTP would be 5.3 months compared with 6.3 months, and the estimated hazard ratio would be only 0.46 ($P = 0.092$). This result is more consistent with the analysis of PSAAdT, indicating only a trend toward an effect.
The measurement of the sex hormone and IGF-I/IGFBP-3 levels during this study may reveal why these interventions were not more successful. During step 1 of the intervention, there was a significant decrease in free testosterone levels, consistent with previous observations in different patient populations (19, 20). However, free testosterone levels remained in the normal range, so that it is possible that the magnitude of the decline was not sufficient to affect clinical progression. Furthermore, during step 1 there was a trend toward increased levels of bioavailable IGF-I. Increased levels of IGF-I are associated with an increased risk of prostate cancer and may promote progression of the disease (15, 16).

During step 2 of the study there was a statistically significant increase in serum IGF-I levels that was not offset by a corresponding increase in IGFBP-3. This increase was unexpected, although soy supplements have been shown recently to increase serum IGF-I levels in premenopausal women (11). Nonetheless there was an unexpected trend toward an increase in IGF-I even during step 1 in this study. Furthermore, although there was a trend toward reduced levels of total testosterone during step 2, there was no effect on the more biologically important free testosterone levels. Therefore, any beneficial effects from the dietary intervention during step 2 appear to override the negative impact of the IGF-I rise. This might have been a result of other hormonal changes or the direct effect of isoflavones on cancer cell growth through various mechanisms, such as inhibition of tyrosine kinase signaling (25, 26).

Overall, the dietary interventions in this study had only modest effects on clinical end points. These results are consistent with the minimal effects observed with low-fat dietary intervention on surrogate end points for breast (27) and colon (28) cancer. Although patients made a significant change in their fat intake, as a group they did not meet the compliance criteria established in this study. Better compliance to the low-fat diet might have resulted in a more favorable outcome. Soy supplementation may be useful, but might be of greater benefit if combined with strategies to reduce IGF-I levels. It is also possible that other dietary changes, such as greater soy intake or soy in a different form such as fermented soy, might be more beneficial. In addition, lycopene, zinc, or even a rigorous exercise program may prove to be of benefit. In a recently published 10-patient pilot study, the authors reported that a complex intervention including a high fiber plant-based diet combined with a stress reduction program, resulted in a significant delay in PSA progression during a brief 4-month trial period (29). However, the majority of the presstudy PSA values were extremely low (<1 ng/ml), making interpretation of PSA doubling time problematic.

Modest effects from this strategy might also be because it is better suited for prevention rather than as a treatment for prostate cancer. The genetic program and microenvironment of the prostate cancer cell may be quite different from that of the normal prostate epithelium at risk for transformation. Against this possibility (and consistent with our initial hypothesis) are animal studies that suggest that even for established tumors, dietary changes affect prostate growth (25, 30).

The number of prostate cancer patients taking alternative therapies, including experimental diets, is increasing substantially. Interest in these kinds of therapies has been fostered by the apparent utility of PC-SPES (31, 32), and data regarding diet and prostate cancer risk. The approach outlined in this study might prove useful toward prolonging the time until androgen ablative therapies are instituted, but the results of this study are modest. This study demonstrates the need to formally investigate “alternative” interventions, rather than adopt them in the clinic based on their inferred value from animal models or epidemiological data on prostate cancer prevention. Also, as emphasized by the unexpected increase in IGF-I levels during both steps in the study, even seemingly benign dietary alterations might have unintended potentially negative consequences on prostate cancer growth.

REFERENCES


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