Dietary intervention after definitive therapy for localized prostate cancer: results from a pilot study

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Introduction: *Diet has been linked to prostate cancer risk. Dietary modification may inhibit prostate cancer progression.*

Materials and methods: *As part of a randomized trial, we analyzed the effect of a diet based intervention on 25 prostate cancer patients who had previously undergone surgery or radiation.*

Results and conclusions: *In the intervention arm, vegetable intake increased ($p < 0.05$), fat intake decreased ($p < 0.05$), and mean plasma levels of ß-carotene and total carotenoids increased ($p < 0.05$). In the control arm, there were no significant changes in diet or blood carotenoids. These data support the feasibility of studying dietary interventions as salvage or adjuvant therapy after surgery or radiation for localized prostate cancer.*

Key Words: diet, surveillance, broccoli, lycopene, crucifer, surgery, radiation, radical prostatectomy, brachytherapy

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Introduction

Up to 50% of newly diagnosed prostate cancer patients present with clinically localized disease;[1] most receive definitive therapy with surgery or radiation.[2] The estimated incidence of prostate-specific antigen (PSA) recurrence following definitive therapy, 70000 patients per year,[3] corresponds to a likely United States population prevalence of at least several hundred thousand. The scope of this problem calls for the development of innovative therapies to treat PSA only recurrence.

Rapid PSA rises following definitive therapy, measured as low PSA doubling times (PSADT), are associated with increased prostate cancer specific

mortality.[4,5] Most investigators agree that patients with rapidly rising PSA following definitive therapy are candidates for local and systemic salvage therapies.

However, most patients with PSA only recurrence do not experience rapidly rising PSA; rather, these patients evince slow rises and prolonged, asymptomatic clinical courses.[4] Although salvage therapies—including radiation, radical prostatectomy, cryosurgery, and androgen deprivation—potentially increase progression free survival after definitive therapy in select patients,[3,6] they are also associated with side effects that may substantially diminish quality of life. Moreover, there is scant evidence to support definitive survival benefits for salvage therapy in patients with slowly rising PSA.

A novel approach with minimal toxicity is dietary modification. Epidemiological studies suggest that diets high in vegetables and low in fat, meat, and dairy products may protect against prostate cancer and decrease the risk of progression.[7-9] In vitro models demonstrate that components of cruciferous vegetables (isothiocyanates) and tomatoes (lycopene) induce apoptosis of prostate cancer cells, inhibit carcinogenesis, and promote the expression of cytoprotective enzymes.[10-12]

Clinical evidence supporting these observational and preclinical findings remains limited. In the only dietary study to date in patients with PSA recurrence after definitive therapy, PSADT significantly increased 6 months after patients began a program of diet modification and stress reduction.[13] However, this study was small and nonrandomized and included substantial lifestyle modifications. Thus, these results cannot with certainty be attributed to changes in nutritional intake. Further studies of dietary interventions for PSA recurrence are needed, particularly since many prostate cancer patients are already experimenting with diet and dietary supplements.[14,15]

We previously designed and implemented a telephone based dietary intervention for breast cancer patients; the intervention produced significant, long lasting diet changes in these patients.[16] We adapted this method for men with prostate cancer and tested it in a randomized, multicenter pilot trial: The Men's Eating and Living (MEAL) Study.[17] To evaluate the feasibility of studying diet based interventions following definitive therapy for prostate cancer, we analyzed the efficacy of this intervention to effect diet change in a cohort of MEAL participants who had undergone surgery or radiation.

Materials and methods

Participants

The MEAL Study was conducted at four clinical sites of the Cancer and Leukemia Group B Cooperative Study Group: The James Cancer Center of Ohio State University, the Southern Medical Oncology Consortium, the Moores UCSD Cancer Center of the University of California at San Diego, and the Roswell Park Cancer Institute (RPCI). The major enrollment sites were UCSD and RPCI. Institutional review board approval was obtained at all study sites.

Eligible patients were men aged 50 to 80 years with biopsy proven prostate cancer. Other inclusion criteria were no history of other malignancy (other than nonmelanoma skin cancer) in the previous 5 years and life expectancy ≥ 3 years. Exclusion criteria included psychiatric illness precluding compliance with the intervention and/or obtainment of informed consent; medical conditions that would make the protocol unreasonably hazardous; intolerance to cruciferous vegetables and/or tomato products; and metastatic prostate cancer.

A total of 74 prostate cancer patients were recruited between March 2005 and March 2006. Of these, 25 (34%) had undergone prior treatment with surgery or radiation. Data collection was completed November 30, 2006.

Study design

MEAL was a 6 month, randomized, controlled clinical trial. The randomization ratio was 2:1 (intervention to control). Participants were randomized to an intervention of structured dietary education and telephone based counseling promoting seven or more servings of vegetables a day, with decreased fat and red meat intake; or to a control condition that provided print materials with standard guidelines recommending five servings of vegetables and fruits daily (U.S. Department of Agriculture, National Cancer Institute, and American Cancer Society). All counseling, performed by telephone from the Moores UCSD Cancer Center, utilized a stepwise, phased approach employing social cognitive theory and motivational interviewing techniques as previously described.[17]

Outcomes assessment

Diets were evaluated at baseline and 6 months, each by a series of three separate 24 hour dietary recalls collected interactively via telephone interview. Data were catalogued and analyzed utilizing Minnesota Nutrition Data System (NDS) software (Nutrition

Coordinating Center, University of Minnesota). Blood samples were collected at baseline and at 6 months and analyzed for plasma carotenoid and serum PSA concentrations. The primary outcome variables were the differences in dietary intakes and plasma carotenoid concentrations between baseline and 6 months (within and between groups).

Statistical analyses

Changes in mean self reported intake of total vegetables, cruciferous vegetables, tomato products, lettuce and potatoes, other vegetables, fruit, whole grains, beans/legumes, fiber, and fat were compared using paired *t* tests within each group and two sample *t* tests between groups. Baseline carotenoid values, log transformed to improve normality, were examined for group differences. Changes in measured plasma α-carotene, ß-carotene, lutein, lycopene, ß-crytoxanthin, and total carotenoids were compared using paired *t* tests within each group and two sample *t* tests between groups.

Results

Participants

Of the 25 participants who had undergone prior surgery or radiation, 17 (68%) had undergone radical prostatectomy, 5 (20%) radiotherapy with androgen deprivation, and 3 (12%) brachytherapy, Table 1. Three (12%) were lost to follow up prior to 6 month data collection, Figure 1.

Dietary changes: vegetables

Vegetable intakes in the intervention arm increased significantly at 6 months, while those in the control arm remained static, Table 2. In the intervention arm, mean daily intakes of total vegetables, crucifers, tomato products, and other vegetables increased by 70%, 52%, 237%, and 45%, respectively, while lettuce and potato intake decreased by 61% ($p < 0.05$). In the control arm, there were no significant changes in mean intakes of total vegetables, tomato products, crucifers, lettuce and potatoes, or other vegetables. Compared

TABLE 1. **Prostate-specific antigen concentrations at baseline and 6 months among patients who had undergone surgery or radiation in the Men's Eating and Living (MEAL) Study.**

Primary therapy	PSA		Group
	Baseline	6 month	
Brachytherapy	2.43	1.74	Control
Brachytherapy	α0.08	0.07	Control
Brachytherapy	0.66	1.06	Control
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	N/A	N/A	Control
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.48	0.55	Intervention
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.03	0.03	Control
Prostatectomy	0.12	0.14	Control
Prostatectomy	N/A	N/A	Intervention
Prostatectomy	0.03	0.03	Intervention
Prostatectomy	0.03	0.05	Intervention
Radiotherapy with androgen deprivation	N/A	N/A	Control
Radiotherapy with androgen deprivation	14.07	20.47	Intervention
Radiotherapy with androgen deprivation	0.33	0.41	Control
Radiotherapy with androgen deprivation	0.19	0.04	Intervention
Radiotherapy with androgen deprivation	0.25	0.13	Control

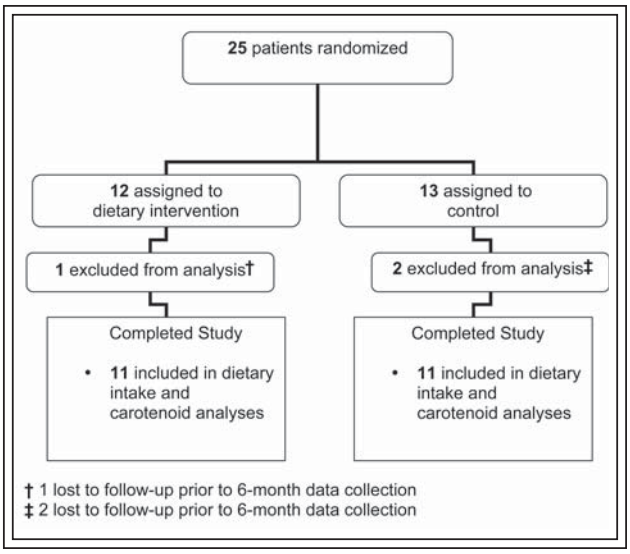

Figure 1. Flow diagram for patients treated with surgery or radiation in the Men's Eating and Living (MEAL) Study.

to control, the increases in total vegetables, tomatoes, and other vegetables in the intervention arm were significant ($p < 0.05$).

Dietary changes: fat

Fat intake decreased by 17% ($p < 0.05$) in the intervention arm and remained stable in the control arm, Table 2.

Plasma carotenoid concentrations

Carotenoid concentrations increased in the intervention arm but not in the control arm, Table 3. At baseline, plasma total carotenoid concentrations of intervention and control participants were similar. At 6 months, the mean total concentration had risen in intervention participants by a significant 19% ($p < 0.05$) and in controls by a nonsignificant 2%. In the intervention arm, the mean ß-carotene concentration increased by 35% ($p < 0.05$), while mean concentrations of α-carotene, lutein, lycopene, and cryptoxanthin concentrations did not change significantly. In the control arm, there were no significant changes in any of the carotenoids measured, Table 3.

PSA concentrations

Plasma PSA concentrations at baseline and 6 months were available for 22 of the 25 participants, Table 1. There were only 10 patients with PSA levels that changed across the three treatment types and two study conditions. Thus, the small size of the dataset precluded definitive quantitative analyses of PSA.

TABLE 2. **Vegetable intakes and nonvegetable mean intakes at baseline and 6 months assessed by using 24 hour dietary recall among patients who had undergone surgery or radiation in the Men's Eating and Living (MEAL) Study.**

	Intervention			Control		
	Baseline (n = 12)	**6 months (n = 11)**	**Change**	**Baseline (n = 13)**	**6 months (n = 11)**	**Change**
Total vegetables[1]	3.3	5.6	70%[2,3]	4.0	3.5	-5%
Cruciferous vegetables[1]	0.9	1.2	52%[3]	0.3	0.3	15%
Tomatoes[1]	0.8	2.7	237%[2,3]	1.0	0.5	-22%
Lettuce and potatoes[1]	0.6	0.3	-61%	0.6	1.0	40%
Other vegetables[1]	1.9	2.6	45%[2,3]	2.4	2.1	-9%
Fruit[1]	3.2	2.4	-31%[3]	2.8	1.8	-32%
Whole grain[1]	1.3	2.4	86%[2,3]	1.2	0.7	-48%
Beans[1]	0.3	1.1	205%[2,3]	0.2	0.1	-32%
Fiber (g/day)	25.8	36.9	42%[2]	25.9	17.9	-31%[3]
Fiber (g/1000 kcal)	12.2	18.3	46%[2,3]	11.9	10.1	-9%
Fat (% energy)	33.2	26.4	-17%[3]	38.3	37.0	-2%

[1]Servings per day
[2]Significant difference ($p < 0.05$) between groups
[3]Significant difference ($p < 0.05$) within group

TABLE 3. **Plasma carotenoid concentrations at baseline and 6 months among patients who had undergone surgery or radiation in the Men's Eating and Living (MEAL) Study.**

Carotenoid (mmol/l)	Intervention (n = 11)			Control (n = 11)		
	Baseline	6 months	Change	Baseline	6 months	Change
α-Carotene	0.17	0.21	24%	0.16	0.16	-2%
ß-Carotene	0.60	0.81	35%[1]	0.63	0.60	-4%
Lutein	0.49	0.55	12%	0.42	0.45	8%
Lycopene	0.83	0.93	12%	0.77	0.77	0
Cryptoxanthin	0.15	0.16	7%	0.15	0.18	23%
Total carotenoids	2.25	2.66	19%[1]	2.13	2.17	2%

[1]Significant difference ($p < 0.05$) within group

Discussion

Assessing the clinical efficacy of dietary change in prostate cancer patients requires carefully designed clinical trials focused on feasible dietary interventions. The intensive lifestyle modifications and face-to-face counseling employed in prior interventions[13,18] require substantial resource commitments that may be difficult to implement and sustain in larger patient populations. In contrast, the intervention we describe is practicable, easy to implement, and centralized. It demands few resource commitments and is relatively low cost, even for relatively large study samples.

To our knowledge, this is the first clinical trial to investigate the application of a validated, diet based intervention as a potential form of adjuvant or salvage therapy for prostate cancer following definitive therapy for localized disease. These pilot data suggest that telephone based counseling emphasizing a plant based diet significantly increases vegetable intake, decreases fat intake, and increases plasma concentrations of potentially anticarcinogenic carotenoids in prostate cancer patients who have previously undergone definitive local therapy.

This intervention focuses on dietary components associated with decreased prostate cancer incidence and progression. The telephone counseling protocol focused on helping men set serial dietary change goals that were achievable within their lifestyle (sometimes their spouse was on the phone as well).[19] Counselors also framed positively[20] the effort put into achieving these goals so as to optimize self efficacy.[21] Patient centered counseling approaches were used to maintain motivation,[2] to modify lifestyles for longer term inclusion of these dietary changes, and to promote retention in the study. A similar program has produced significant diet changes and plasma carotenoid increases for at least 4 years in more than 1500 breast cancer patients who continued periodic counseling.[16]

Diet change represents an innovative approach to refining current treatment paradigms for PSA only recurrence after definitive therapy. It is unclear whether the morbidities of salvage therapies outweigh potential survival benefits in patients with less aggressive disease as indicated by longer PSADT. In this sense, a plant based dietary intervention represents a compelling salvage option for these patients. Other potential applications of this dietary intervention are as adjuvant treatment in patients with low- to intermediate-risk disease, adjuvant treatment in patients with high-risk disease who decline more aggressive forms of therapy, and primary treatment in active surveillance.

Prostate cancer diagnosis is a source of considerable anxiety and diminished quality of life for many prostate cancer patients, even after definitive therapy.[22-24] Dietary change could quell anxiety, improve quality of life, and encourage men with higher PSADT and no other clinical signs of progression to eschew or delay adjuvant, morbidity generating therapies with unproven survival benefits. Since these patients are usually asymptomatic, they would likely be receptive to nutritional interventions with proven benefits to cardiovascular and overall health. Indeed, it is likely that many—if not most—older patients with a slow rising PSA will die of cardiovascular disease rather than metastatic prostate cancer. Future dietary intervention trials should thus consider major coronary events (myocardial infarction, coronary artery bypass surgery, angioplasty, and stroke) as important secondary endpoints.

Although dietary self reporting methods may be susceptible to systematic measurement error,[25] plasma carotenoid concentrations are an effective biomarker for dietary intake of carotenoids and serve as an objective indicator of a vegetable intense diet.[26] The increases in blood carotenoid concentrations in the intervention patients validate the participant reported dietary changes. Moreover, carotenoids have been associated with reduced risk of incident prostate cancer[27,28] and diminished oxidative damage in prostate tissue.[29] Total carotenoid concentrations increased 19% in the intervention group. However, there was not a significant increase in plasma lycopene, even though these men reported major increases in tomato consumption. In observational and feeding studies that have examined the relationship between vegetable and fruit intake and plasma carotenoid concentrations, lycopene is typically not as responsive to or as correlated with vegetable and fruit intake, compared to the other carotenoids.[30] Compared to the other carotenoids, lycopene is found in abundance in few foods—mainly tomatoes and tomato products, watermelon, and pink grapefruit—and when these foods are consumed in raw form, the concentration and dosage is relatively low because of the dilution factor. When cooked, such as in the production of tomato sauce or paste, the amount of lycopene per serving is increased, which explains why those cooked and concentrated sources typically are more predictive of plasma lycopene concentration than raw tomatoes or overall vegetable and fruit intake.[31]

Two limitations of this analysis merit discussion. First, these results do not prove that the changes in diet intake and plasma carotenoid concentrations observed over a 6 month period will be maintained over a longer period of time. Nevertheless, our experience with the prior study in breast cancer patients[16] suggests that diet changes observed in the first 6 months of the MEAL intervention could be maintained for at least 4 years should the intervention continue.

Second, these results do not prove that changes in diet and plasma carotenoid concentrations will necessarily alter the natural history of PSA only recurrence. Our intent in this feasibility study was to test whether a telephone based counseling intervention would produce diet and plasma carotenoid changes in prostate cancer patients, including those who have previously undergone definitive local therapy—not to assess whether these changes would alter clinical progression. The rationale for trials of diet intervention and prostate cancer is driven not only by the possibility that diet plays a significant role in prostate cancer carcinogenesis, but also by the widespread desire of patients to know whether dietary change has any value in disease control.

In summary, these data support the feasibility of implementing clinical trials of dietary interventions in men with prostate cancer following definitive therapy. Our findings warrant additional randomized clinical trials to further test this intervention. Future, larger studies should utilize PSA changes as a primary endpoint to test the hypothesis that telephone based diet changes will diminish disease progression and the need for conventional salvage or adjuvant treatments in these patients. □

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