0022-5347/01/1666-2202/0
THE JOURNAL OF UROLOGY®
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Vol. 166, 2202–2207, December 2001
Printed in U.S.A.

CAN DIET IN CONJUNCTION WITH STRESS REDUCTION AFFECT THE RATE OF INCREASE IN PROSTATE SPECIFIC ANTIGEN AFTER BIOCHEMICAL RECURRENCE OF PROSTATE CANCER?

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ABSTRACT

Purpose: Epidemiological and laboratory evidence indicates that a Western diet is associated with an increased incidence of prostate cancer. Specific components of the diet, such as high saturated fat, low fiber and high meat content, may have greatest clinical significance in the later stages of tumor promotion and progression. However, departure from the conventional diet is difficult to initiate and maintain. Therefore, we combined the well-known Mindfulness-Based Stress Reduction (MBSR) program with a low saturated fat, high-fiber, plant-based diet to determine the effect on the rate of change in prostate specific antigen (PSA) in patients with biochemical recurrence after prostatectomy.

Materials and Methods: We enrolled 10 men and their partners in a 4-month group-based diet and MBSR intervention. A pre-study post-study design in which each subject served as his own control was used to compare the rate of increase in and doubling time of PSA before and after intervention.

Results: The rate of PSA increase decreased in 8 of 10 men, while 3 had a decrease in absolute PSA. Results of the signed rank test indicated a significant decrease in the rate of increase in the intervention period ($p = 0.01$). Estimated median doubling time increased from 6.5 months (95% confidence interval 3.7 to 10.1) before to 17.7 months (95% confidence interval 7.8 to infinity) after the intervention.

Conclusions: Our small study provides evidence that a plant-based diet delivered in the context of MBSR decreases the rate of PSA increase and may slow the rate of tumor progression in cases of biochemically recurrent prostate cancer. Larger-scale randomized studies are warranted to explore further the preventive and therapeutic potential of diet and lifestyle modification in men with prostate cancer.

KEY WORDS: prostate, prostatic neoplasms, prostate-specific antigen, diet, disease progression

Approximately 35% of men initially treated for prostate cancer have biochemically defined recurrence marked by detectable prostate specific antigen (PSA) elevation within 10 years of definitive local therapy. In more than a third of these men metastatic disease develops within the subsequent 5 years.[1] To our knowledge no curative therapy exists for metastatic prostate cancer. Medical and surgical androgen ablation can produce responses in most patients but with side effects, including osteoporosis, decreased muscle mass and impotence.[2] This finding has motivated a search for novel adjunctive strategies that may retard tumor progression and postpone hormone therapy.

Dramatic international variations in age adjusted incidence and mortality rates, such as an incidence in Qidong County, China of 0.5/100,000 men versus the incidence in the United States of 102.1/100,000[3,4] and approximate host country rates in the grandchildren of Japanese migrants, point to the dominant influence of environmental factors.[3,5,6] Of environmental influences diet may be the most important modifiable risk factor. Total fat and meat consumption is associated with overall incidence of prostate cancer[7–9] as well as with an incidence of more aggressive tumors.[8,9] Saturated fat from meat and dairy intake is the most strongly associated fat subtype.[10,11] Conversely the intake of whole grains and soy products is associated with decreased mortality.[12]

Results from laboratory animal experiments are consistent with these findings. Fat restriction has inhibited the growth of transplanted prostate cancer cells in rodents.[13,14] Fat restriction[5] and the feeding of the soy isolate genestein[15] inhibit growth of the LNCaP human prostate cancer cell line.

Preliminary evidence also indicates that prostate cancer may be sensitive to diet even after metastasis develops. Plant-based diets may be associated with prolonged survival and instances of remission of bone metastasis in men with advanced disease.[16] These findings may be partially explained by the demonstrated ability of low-fat, high-fiber diets to modulate circulating androgen levels.[17,18]

A number of psychosocial factors reinforce dietary habits and must be addressed if a new healthier pattern is to be

Accepted for publication July 27, 2001.
* Recipient of a grant from the University of Massachusetts Cancer Center Our Danny Cancer Fund and Cooperative Agreement U48/CCU409664 from the Centers for Disease Control and Prevention (Dr. Jane Teas, P.I.).
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The contents are solely the responsibility of the authors and do not necessarily represent the official views of either funding agency.

established. Mindfulness Based Stress Reduction (MBSR), an outpatient program developed at University of Massachusetts Medical School, aims through intensive training in mindfulness meditation and its applications in everyday life to enhance healthy attitudinal and behavioral changes in patients with a wide range of stress and pain disorders, and chronic diseases.[19] It has been shown to be effective for decreasing panic disorder and anxiety,[20] and for helping patients to cope with the inevitable personal, family and social conflicts that accompany difficult life style changes.[21] Stress management training generally has been shown to modulate neuroendocrine and neuroimmune pathways,[22,23] and it may have salutary effects on chronic prostatitis,[24] a condition often exacerbated by stress.[25] Furthermore, social support has been associated with increased survival in cases of metastatic breast cancer and malignant melanoma.[26,27] We tested the effect on PSA of an intensive intervention combining dietary change with MBSR after prostatectomy in men after biochemical recurrence of prostate cancer. Each patient served as his own control since the PSA rate of change and doubling time from the end of the nadir period to the beginning of intervention (pre-study period) were compared with those from the beginning to the end of the 4-month intervention (post-study period).

PATIENTS AND METHODS

The study protocol was approved by the University of Massachusetts Medical School Institutional Review Board for use of human subjects in medical research. All participants provided informed consent before being enrolled in the study.

Patients had biopsy confirmed adenocarcinoma of the prostate, underwent radical prostatectomy as primary therapy and subsequently had increasing PSA on at least 2 sequential tests not more than 6 months apart after achieving a posttreatment nadir. They were referred by a network of participating urologists from the University of Massachusetts-Memorial Medical Center, Fallon Clinic and private offices in central Massachusetts. Study exclusion criteria were primary high dose radiation or brachytherapy, postoperative radiation therapy to the prostatic fossa or hormone therapy within 6 months of intervention, more than 1 leuprolide injection during the year before intervention to ensure further against any lingering effect of hormonal therapy on the pre-study PSA rates and co-morbidities that would limit study participation.

This study was a nonrandomized clinical trial providing an intensive intervention integrating dietary change with MBSR. The plant-based diet was nutritionally balanced, low in saturated fat and high in fiber. It focused on whole grains, legumes, fresh green and yellow vegetables, seeds and legumes, soy food and fruit. Processed and refined products, caffeine and foods of animal origin were strictly limited. MBSR was taught as an integral part of the dietary intervention. It included mindfulness meditation training, gentle exercise in the form of yoga and social support.

Each participant received individual dietary counseling and MBSR orientation before the intensive group intervention, which consisted of a series of 12 weekly classes of 3 to 4 hours each. They were required to be accompanied to the classes by a support person, preferably someone with whom they shared food. For 7 of the 10 participants this person was the spouse.

Classes were held in the University of Massachusetts Division of Preventive and Behavioral Medicine demonstration kitchen and adjacent conference room. Each class included a presentation on nutrition information by a trained nutritionist (P. H. R.), instruction and practice in preparing interesting and representative dishes by a vegetarian chef (D. J.), and elements of MBSR training by an instructor (J. F. C.) from the UMass Stress Reduction Clinic. Each class included opportunities for in-depth discussion of any challenges and difficulties that may have arisen in making the recommended changes. Classes were concluded by a shared meal prepared by the participants under the direction of the chef.

Diets were assessed at the beginning and end of the 4-month intervention period for total and saturated fat, carbohydrate, protein, fiber and total caloric intake using the 7-Day Dietary Recall, an instrument that assesses diet with a high level of accuracy.[28] Physical activity assessment was based on responses to ancillary questions on the instrument. Body weight also was assessed at the beginning and end of the intervention period. Height was measured at baseline only.

As the primary study end point, the rate of change in PSA before (pre-study) and during the course of intervention (post-study) were determined and compared. Post-study rates of PSA change were based on serum samples obtained at the beginning and end of intervention using the Immulite 2000 PSA test (Diagnostic Products Corp., Los Angeles, California), a completely automated, ultrasensitive chemiluminescence assay with a sensitivity limit of 0.04 ng./ml. PSA measurements used to determine pre-study comparison rates of PSA change began with the last nadir point after the completion of primary treatment, defined as that point after which there were 2 or more consecutive increases in PSA. They included all subsequent measurements up to the beginning of intervention. PSA measurements from the end of the nadir period to the beginning of intervention, as part of routine patient clinical care, were obtained by reviewing medical records.

Some patient pre-study measurements were made elsewhere using test kits with slightly different performance characteristics than the Immulite PSA test (M. Snyder, personal communication, July 2000). Only a single laboratory was used per patient for determining pre-study slope. When there were pre-study measurements from more than 1 laboratory, values from the most frequently used laboratory were used for analysis. We assumed that rates of change in PSA but not absolute PSA levels were comparable among laboratories.

Linear regression was used to calculate pre-study and

TABLE 1. *Patient age and tumor characteristics*

Pt. No.—Age	TNM Tumor Stage	Gleason Score	Pre-Study Adjunctive Therapy	Pre-Study PSA (ng./ml.)	Mos. Doubling Time	
					Pre-Study	Post-Study*
1—70	T2b	6	Radiation	1.95	7.3	22.4
2—64	T2a	7		0.11	3.5	−13.4
3—70	T2c	6	Hormone	0.84	2.7	6.2
4—56	T4	7		0.07	6.5	6.0
5—65	T2c	9		0.74	3.9	13.1
6—74	TX	6		22.9	7.9	−18.4
7—61	T2b	7		0.40	5.4	12.1
8—69	T2c	5		0.13	6.4	−16.2
9—67	T2b	6		1.56	24.7	11.3
10—78	T3	6		1.43	11.2	44.3

* Negative values indicate decreasing slope and absolute values can be interpreted as halving time.

post-study rates of PSA increase in all men. During periods of rapid proliferation cancer shows log linear, and not simply linear, growth.[29] Therefore, PSA data were log transformed to meet the normality and linearity assumptions of linear regression and these log transformed data form the basis of all results presented. Slopes of log PSA versus time were compared in each subject for pre-study and post-study periods using the signed rank test. Slopes were translated into PSA doubling time using the formula, doubling time = log 2/slope. We calculated median doubling time and the corresponding 95% confidence interval (CI). The association of the change in slope with the change in dietary and life-style factors was estimated using Spearman's rank correlation. Multiple regression analysis was performed to estimate associations after adjusting for pre-slope values.

Additional analysis was also performed to evaluate the possibility of regression to the mean, that is the tendency of high values to be lower on repeat measurement. In 5 men with sufficient PSA values the initial PSA values used for determining selection were not used to estimate pre-study slope. Thus, the effect of regression to the mean was damped. The distribution of slope was simulated using a correlation of 0.6 estimated from the data. Thus, the effect of possible regression to the mean on PSA doubling time was estimated and subtracted from the estimated change in slope.

RESULTS

Table 1 lists ages and disease status of the 10 participants. Two men underwent adjunctive therapy after radical prostatectomy and before study entry, including postoperative radiation to the prostatic fossa and leuprolide administration 2 years and 11 months before intervention. The Gleason score was determined by pathological evaluation of biopsy specimens. In 9 of the 10 patients there was no clinical evidence of local recurrence, while in the remaining patient there was no clinical evidence of recurrence after completing postoperative radiation to the prostatic fossa. Mean time from the last nadir PSA to the beginning of intervention plus or minus standard deviation (SD) was 35.5 ± 35.8 months. The SD was relatively large because intervention began in 1 man 122 months after PSA began to increase. In almost all cases nadir values were identical to the sensitivity threshold of the PSA test (0.04 ng./dl.).

The slope of PSA change decreased in 8 men, including a change to a negative value in 3, indicating an absolute PSA decrease and not only a decreased rate of change. In 2 men it increased when comparing the pre-study and post-study periods (table 2). The signed rank test showed a statistically significant decrease in the slope of the group overall ($p = 0.01$). Analysis accounting for possible regression to the mean provided an upper estimate of any possible effect, which was subtracted from the overall change in the pre-study PSA rate. This adjustment did not affect the number of men with a decreasing slope but it resulted in a slight increase in the p value derived from the signed rank test (adjusted $p = 0.04$). Figure 1 shows paired pre-study versus post-study slope by patient in order of increasing pre-study slope. The post-study slope was negative in 3 men, indicating decreased PSA. For the group overall estimated median doubling time based on slope was 6.5 months during the pre-study period (95% CI 3.7 to 10.1) and 17.7 months during the post-study period (95% CI 7.8 to infinity). The upper limit of the latter CI would be equivalent to a slope of 0 or less, indicating no doubling time, which was the expected result in the 3 men with decreases in PSA.

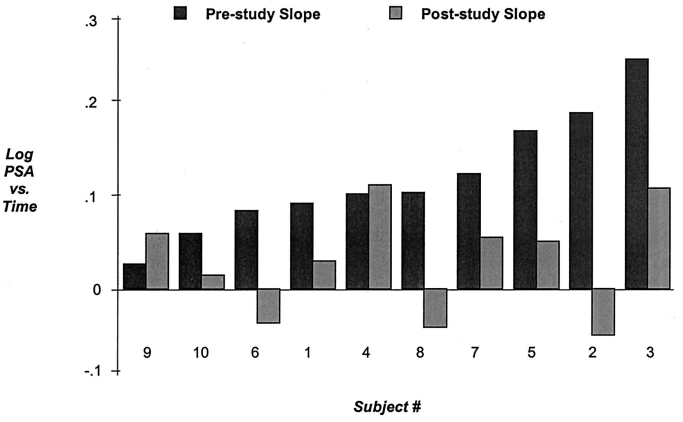

FIG. 1. Pre-study versus post-study PSA slope by patient, ordered according to increasing pre-study slope.

Total fat intake decreased in 6 of the 10 participants. The mean reduction was of 6 gm. daily (table 3). Nine men decreased the saturated fat intake a mean of 4.14 gm. daily. The reduction in saturated fat accounted for 69% of the mean decrease in total fat. Mean caloric intake decreased in 8 cases representing an average of 530 kcal. daily for the group. Mean fiber intake increased by 5.5 gm. daily, representing a 40% increase from baseline, but only 4 of the 10 men increased the fiber intake. In the 2 men in whom caloric intake increased fiber intake increased by 28.6 gm./1,000 kcal. daily. In the remaining 8 men there was an increase per unit decrease in caloric intake of 4.3 gm./1,000 kcal. daily. That is, although absolute fiber intake decreased, the fiber concentration of the diet increased.

The 2 men who increased energy intake also greatly increased the exercise level from 19 to 51 and 18 to 122 daily, respectively. Eight of the 10 patients increased the time spent in intentional physical activity. The average duration increased by 57% from 21 to 33 minutes daily. Body mass index (BMI) was calculated according to the formula, BMI = weight in kg./height in $m.^2$ All 10 men lost weight. The mean decrease in body mass index was 7% from 30.3 to 28.2 $kg./m.^2$, corresponding to an average weight loss of about 6.3 kg.

TABLE 2. *Estimated PSA slope during pre-study and post-study intervention period*

Pt. No.	Slope		Mos. Doubling Time	
	Pre-Study	Post-Study	Pre-Study	Post-Study*
1	0.095	0.031	7.3	22.4
2	0.196	−0.051	3.5	
3	0.256	0.112	2.7	6.2
4	0.105	0.116	6.6	6.0
5	0.176	0.053	3.9	13.1
6	0.088	−0.038	7.9	
7	0.128	0.057	5.4	12.1
8	0.107	−0.043	6.5	
9	0.028	0.061	24.7	11.3
10	0.062	0.016	11.2	44.3
Mean (95% CI)	0.124 (0.076–0.173)	0.031 (0.012–0.075)	6.5 (3.7–10.1)	17.7 (7.8–infinity)

* In 3 patients absolute PSA levels decreased, not just the rate PSA doubling time. A negative post-study slope indicates that if the levels decrease continued, PSA would eventually reach zero.

TABLE 3. *Changes in dietary intake, exercise level and body mass index according to changes in PSA slope*

Pt. No.	PSA Slope*	Fiber Intake (gm./day)	Total Fat Intake (gm./day)	Saturated Fat Intake (gm./day)	Energy Intake (kcal./day)	Exercise Level (min./day)	Body Mass Index (kg./m.^{2})
2	−0.25	39.6	−7.04	0.10	1,179	32	−2.59
8	−0.15	−2.0	−14.23	−4.60	−2,333	24	−2.20
3	−0.14	24.1	0.05	−1.38	1,027	104	−3.95
6	−0.13	3.7	6.78	−2.92	−166	4	−3.91
5	−0.12	−2.1	−2.95	−4.27	−640	39	−1.88
7	−0.07	6.8	−14.16	−5.37	−263	25	−0.92
1	−0.06	−4.4	−33.57	−13.89	−1,190	−6	−0.74
10	−0.05	−1.2	5.46	−0.68	−569	13	−2.59
4	0.01	−2.3	1.68	−1.93	−777	7	−0.89
9	0.03	−7.6	−2.29	−6.43	−1,566	−12	−1.49

* Log PSA versus time.

TABLE 4. *Pre-study and post-study values of significant predictors of changes in PSA slope*

Pt. No.	Fiber Intake (gm./day)		Exercise Level (mins./day)		Body Mass Index (kg./m.^{2})	
	Pre-Study	Post-Study	Pre-Study	Post-Study	Pre-Study	Post-Study
1	6.9	2.5	32	26	29.61	28.87
2	14.1	53.8	19	51	31.30	28.71
3	19.2	43.3	18	122	34.08	30.13
4	12.8	10.6	0	7	29.25	28.36
5	14.9	12.8	19	58	28.82	26.94
6	13.9	17.7	15	19	29.93	26.02
7	6.5	13.3	25	50	31.00	30.08
8	21.6	19.6	18	42	31.16	28.96
9	14.6	7.0	51	39	29.67	28.18
10	12.7	11.5	13	26	28.65	26.06

PSA slope showed that 3 measured changes in dietary and life-style factors were statistically significantly associated with the change in the rate of increase in PSA during the course of intervention (table 4). The strongest relationship, which was an inverse association, was with dietary fiber intake (Spearman's $\rho = -0.73$, $p = 0.02$). The change in the rate of increase also was inversely related to the change in the number of minutes of exercise (Spearman's $\rho = -0.60$, $p = 0.04$). The change in the rate of increase was positively associated with the change in body mass index (Spearman's $\rho = 0.60$, $p = 0.04$). Figure 2 shows dietary fiber, exercise level and body mass index versus the change in PSA slope, respectively. The change in PSA slope also was related to the pre-slope (Spearman's $\rho = -0.71$, $p = 0.02$), as were the life style factors. When adjusted for pre-slope values, none of the dietary and lifestyle factors showed a statistically significant association.

DISCUSSION

We observed that in men with increasing PSA after radical prostatectomy a program of structured dietary change integrated with MBSR training resulted in a significantly decreased rate of PSA increase, an almost 3-fold increase in PSA doubling time (although the CI was large because of small sample size) and an absolute decrease in PSA in 3 men. Moreover, changes produced by the intervention, including increased dietary fiber intake and exercise level, and decreased body weight, were specific predictors of these outcomes. Unlike most existing or proposed treatment strategies this intervention directly addresses risk factors that can be modified by patients and has no known adverse side effects. Moreover, it uses a novel integration of a meditative mind/body orientation based on the cultivation of mindfulness and encompassing all aspects of the dietary change intervention, such as shopping, food preparation, eating, and experiencing emotions after eating. These elements may increase motivation and intervention compliance. The potential health benefits of this approach include enhanced quality of life and simultaneous decrease in risk factors for co-morbidities that are common in older men, such as cardiovascular disease and diabetes. Furthermore, because the intervention involved other members of each patient support group, most notably the spouse, its effect would be expected to be more durable than one aimed only at the study participant.

What is the mechanism of a possible effect of this intervention on prostate cancer progression? The dietary fiber, exercise, and body weight relationships with PSA doubling time indicate a common endocrine mechanism. Vegetarians consume more dietary fiber and have lower serum testosterone and 17β-estradiol than nonvegetarians.[30] A low-fat, high-fiber diet combined with exercise and weight loss also has been shown to increase sex hormone-binding globulin and, therefore, would decrease the ratio of free-to-bound testosterone.[18] Decreased availability of biologically active free testosterone for binding by testosterone receptors may lead to decreased prostate cancer cell proliferation.

While dietary and lifestyle changes may make theoretical sense, it is often argued that they are impractical and patients may not comply with the changes they are asked to make. Not all participants complied with the diet and lifestyle recommendations to the same degree and we cannot be certain that the changes that they made are enduring. Nevertheless, most men made significant behavioral changes and all attained significant weight loss in a relatively short period. The combined effect of the changes in dietary factors and exercise levels was consistent with reported decreases in caloric intake and increases in exercise levels.

According to the Health Belief Model people modify behavior when they believe that there may be serious consequences if behavior is not modified, they are capable of taking action to change behavior, changing behavior decreases risk and the potential cost of taking action are outweighed by the benefits. All study participants knew that they were in the early stages of recurrent prostate cancer, a condition with no known cure and limited treatment options. A number had co-morbidities, such as heart disease and diabetes, demanding commitment to the same set of dietary and lifestyle changes. Participation was encouraged by their urologists and supported by their partners. In addition, MBSR may have helped them to recognize and work through feelings of loss and helplessness. It also may have assisted them to identify and address self-defeating behavioral patterns and

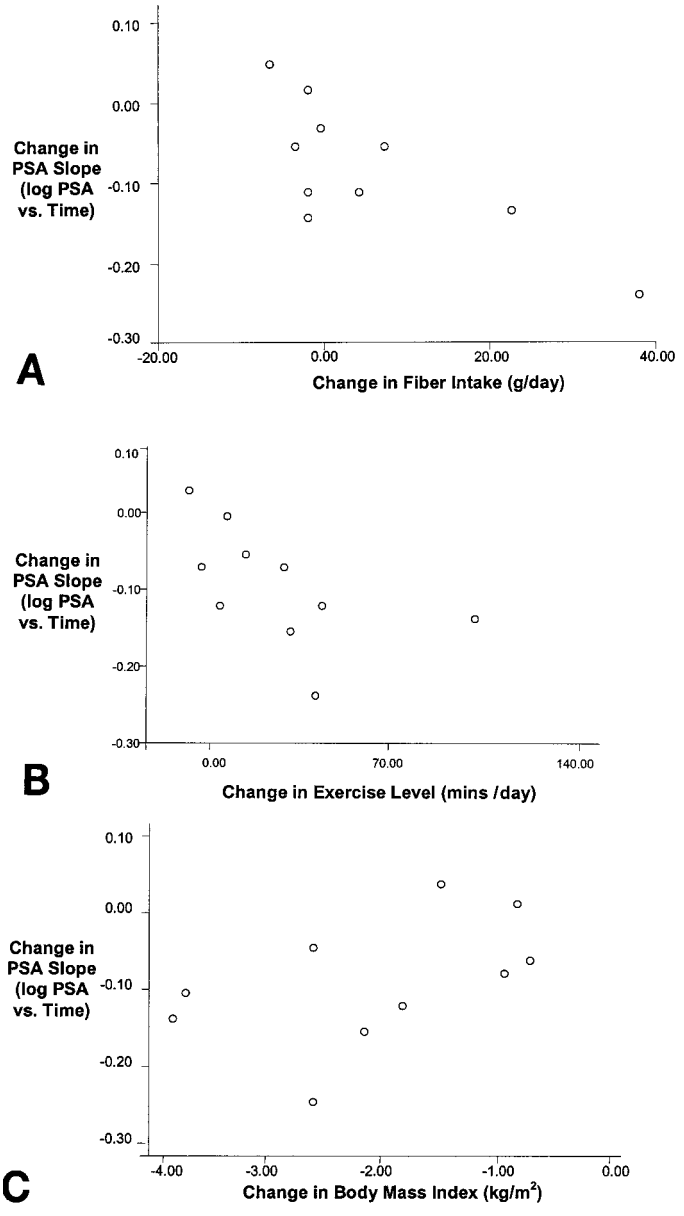

FIG. 2. Changes as predictor of change in PSA slope. *A*, fiber intake. *B*, exercise level. *C*, body mass index.

mobilize the innate capacity for self-healing. They made these changes in the context of a group with a common health concern and a difficult lifestyle transition. They were supported and encouraged by a dedicated, compassionate and highly trained staff. Furthermore, positive reinforcement for change was provided by nonprostate cancer related health benefits that they reported, such as improved blood pressure, serum glucose and cholesterol, decreased medication requirements, increased energy levels, decreased pain and enhanced well-being.

Our study had several important limitations. The most obvious of these was the small sample size of 10 participants and the lack of randomization. Partially because of small sample size we did not completely differentiate the effects of dietary factors from each other or from other aspects of intervention. Thus, it was difficult to gauge the possible specific effects of these components or assess possible interactions with dietary factors. These questions should be the focus of future inquiry.

The 4-month period may have been too short for some patients to achieve and maintain for a prolonged time the desired level of dietary and lifestyle change. A longer interval of sustained adherence may be required to maximize the biological impact of intervention on PSA. Because of the relationships of pre-slope PSA with PSA change and lifestyle factors associated with the PSA change, adjusting for pre-slope values may have represented inappropriate over control for these factors. While regression to the mean does not appear to have biased results to a large extent in these data, future work must focus on the need to control background PSA or some other indicator of disease progression in the study design, perhaps by blocking randomization on this variable.

While it is biologically feasible that this intervention may decrease disease progression, this interpretation must be made cautiously because we did not assess tumor progression directly, relying instead on the surrogate marker PSA. When the recurrent prostate cancer diagnosis is based only on a PSA increase, the extent of spread is often unclear. However, a post-prostatectomy PSA increase usually signifies recurrent prostate cancer and the rate of the PSA increase correlates closely with the rate of prostate cancer growth.[31] Also, in patients with hormone refractory disease undergoing chemotherapy or other nonhormonal therapy a decrease of greater than 50% from baseline PSA is associated with increased survival.[32] Although it is likely that most, if not all, men had recurrence, none had clinical, bone scan or magnetic resonance imaging evidence of metastasis. As a result, we did not ascertain whether or in whom these presumed recurrences represented local, regional or distant disease. We did not compare absolute PSA among laboratories. It is difficult to estimate whether or in what way it may have biased our findings. Furthermore, 1 man underwent radiation therapy and 1 received leuprolide postoperatively. While we did not enroll in our study men who had recently (within 6 months of intervention) undergone these therapies, it also is not clear whether or how these followup treatments may have affected the subsequent rate of PSA change.

CONCLUSIONS

Dietary change combined with mindfulness training significantly slowed the rate of increase in PSA in men with biochemical or PSA recurrence after radical prostatectomy. Doubling time increased from a median of 6.5 months before to 17.7 after the study. All 10 men lost weight, averaging 7% in the whole group. PSA decreased in 3 men. Furthermore, changes associated with the intervention, including increased dietary fiber intake and exercise level, and decreased body weight, were specific predictors of these outcomes. Small sample size and the lack of randomization limited our study. Although findings in self-selection trials have great clinical relevance, future randomized large-scale studies are warranted to explore possible biological mechanisms and, using direct assess the effectiveness and clinical applicability of diet and lifestyle intervention using direct prostate cancer end points.

Drs. Douglas Dahl and Yunsheng Ma, Barbara Olendzki and Elana Rosenbaum contributed to this study.

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