Clinical Events in Prostate Cancer Lifestyle Trial: Results From Two Years of Follow-Up

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OBJECTIVES Previous research has demonstrated that patients with prostate cancer participating in the Prostate Cancer Lifestyle Trial had a reduction in prostate-specific antigen (PSA) levels, inhibition of LNCaP cell growth, and fewer prostate cancer-related clinical events at the end of 1 year compared with controls. The aim of this study was to examine the clinical events in this trial during a 2-year period.

METHODS The Prostate Cancer Lifestyle Trial was a 1-year randomized controlled clinical trial of 93 patients with early-stage prostate cancer (Gleason score <7, PSA 4-10 ng/mL) undergoing active surveillance. The patients in the experimental arm were encouraged to adopt a low-fat, plant-based diet, to exercise and practice stress management, and to attend group support sessions. The control patients received the usual care.

RESULTS By 2 years of follow-up, 13 of 49 (27%) control patients and 2 of 43 (5%) experimental patients had undergone conventional prostate cancer treatment (radical prostatectomy, radiotherapy, or androgen deprivation, $P < .05$). No differences were found between the groups in other clinical events (eg, cardiac), and no deaths occurred. Three of the treated control patients but none of the treated experimental patients had a PSA level of ≥10 ng/mL, and 1 treated control patient but no treated experimental patients had a PSA velocity of >2 ng/mL/y before treatment. No significant differences were found between the untreated experimental and untreated control patients in PSA change or velocity at the end of 2 years.

CONCLUSIONS Patients with early-stage prostate cancer choosing active surveillance might be able to avoid or delay conventional treatment for at least 2 years by making changes in their diet and lifestyle. UROLOGY 72: 1319–1323, 2008. © 2008 Elsevier Inc.

In the United States, prostate cancer is the most common type of noncutaneous cancer in men.[1] The widespread use of serum prostate-specific antigen (PSA) screening and the use of extended pattern biopsy has resulted in considerable prostate cancer stage or risk migration, with many men diagnosed with limited-volume, low-grade disease of uncertain biologic significance. Although a number of effective treatments for prostate cancer exist, these treatments can result in many unpleasant side effects, including urinary incontinence and sexual dysfunction, which are associated with a reduction in quality of life.[2] Because of these side effects, and because low-grade prostate cancer is a slow-growing cancer with a low death rate, some men with early-stage prostate cancer and their physicians are opting to withhold conventional treatment and to adopt a "watch and wait" approach (ie, active surveillance).[3]

Given that evidence is growing from epidemiologic, migrant, and animal studies that implicates lifestyle in the role of prostate cancer,[4-9] many patients are making changes to their diet and lifestyle in an effort to slow or reverse the progression of their disease. To study the effectiveness of such changes, the Prostate Cancer Lifestyle Trial (PCLT) randomly assigned 93 men with early-stage prostate cancer (who had opted for active surveillance before the study) to either a 1-year intensive lifestyle change program or to a usual care control

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group.[10-13] The results of that study found that at the end of the 1-year program, the patients in the experimental group had had a significant reduction in PSA level and had had fewer prostate cancer-related clinical events compared with the controls. Also, after 1 year, the growth of LNCaP prostate cancer cells was inhibited almost 8 times more in the serum from the experimental than in that from the control group (70% vs 9%, $P < .001$).[11] However, whether these lifestyle changes affected clinical events (eg, conventional prostate cancer treatment, cardiac events) after 1 year is unknown. The aim of this study was to examine the clinical events in the PCLT at 1 year after the intervention.

MATERIAL AND METHODS

Participants

The PCLT consisted of 93 men (mean age 66 ± 8 years) with biopsy-proven prostate cancer (Gleason score <7, PSA 4-10 ng/mL) who had chosen active surveillance and had been randomly assigned to either an experimental or a control group. The experimental group had been prescribed an intensive lifestyle program that included a vegan diet (supplemented with soy,[14] fish oil, vitamin E, selenium, and vitamin C), moderate aerobic exercise (walking 30 minutes 6 days weekly), stress management techniques (gentle yoga-based stretching, breathing, meditation, imagery, and progressive relaxation for a total of 60 minutes daily) and participation in a 1-hour weekly support group to enhance adherence to the intervention.[15] The diet was predominantly fruits, vegetables, whole grains (complex carbohydrates), legumes, and soy products, was low in simple carbohydrates, and included approximately 10% of calories from fat.[11,16] The control group patients received the usual care.

The details of the PCLT recruitment, methods, and patient characteristics have been previously reported.[10-13] In brief, of the 181 patients who were eligible for the study, 93 enrolled, including 44 in the experimental group and 49 in the control group. The reasons for refusal to participate were an unwillingness to make or not make the comprehensive lifestyle changes and/or a refusal to undergo periodic testing. All medical decisions, including whether and when to undergo conventional treatment of their prostate cancer, were deferred to each patient's personal physician. The baseline characteristics of these 93 patients were similar to those of active surveillance patients in other studies (eg, age, marital status, PSA level),[17,18] and no baseline differences were present between the experimental and control patients.[11]

Outcome Measures

Clinical Events. A clinical event was defined as the receipt of conventional treatment of prostate cancer (eg, radiotherapy); experiencing a life-threatening event (eg, myocardial infarction); a diagnosis of a serious comorbidity (eg, other cancer); undergoing surgery or a procedure (eg, transurethral resection of the prostate); a medical problem requiring hospitalization (eg, gastrointestinal bleeding); or a medical problem requiring a visit to the emergency room (eg, chest pain).

To assess the clinical events, we reviewed 2 sources of patient data: the study chart and the Health Events questionnaire. The study chart contained the records of all communications that occurred between the patient and the study staff, including quarterly telephone calls and mailings made to all patients. The Health Events questionnaire asked patients to indicate whether they had received any treatment of prostate cancer or had been to any hospital for a procedure, an emergency room visit, or an overnight stay since the study had begun. In the event that a participant could not complete the Health Events questionnaire, his next of kin was asked to complete the questionnaire on the patient's behalf or the health events were determined solely from the study chart review. After the clinical events were identified, the medical records were requested from the patients' physicians.

Additional Variables. The serum PSA and plasma lipids and lipoprotein levels were measured at baseline and at 3-month intervals for 24 months. The serum PSA level was measured prospectively by a heterogeneous sandwich magnetic separation assay with the Immuno 1 System at Memorial Sloan-Kettering Cancer Center (New York, NY). Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were measured at Unilab (Sacramento, CA; see Ornish et al.[11] for more details).

To assess the patients' quality of life and the degree of adherence to the lifestyle program, a battery of instruments (including the Sexual Function Subscale of the University of California, Los Angeles, Prostate Cancer Index, Perceived Stress Scale, and Medical Outcomes Study Short Form-36), described previously,[13] were administered at baseline and 1 year after the study began[13] and were re-administered at year 2. Adherence consisted of self-reported diet, exercise, and stress management behaviors that were used to compute an index of adherence to the lifestyle program. Adherence could range from 0% to >100%, if the person exceeded the recommended program goals.[13]

Statistical Analysis

Fisher's exact tests were performed to compare the number of experimental patients with the number in the control group who experienced clinical events by the 24-month point. PSA velocity was calculated using the slope from a linear regression analysis, using all available measurements. To assess for group differences in PSA velocity, independent samples t tests were performed. Repeated measures analysis of variance were computed to assess for group differences in the changes from baseline to 24 months for the remaining continuous variables.

RESULTS

Clinical Events

Information on clinical events was obtained for 92 of the 93 patients (99%). Event data were missing for 1 experimental patient. For 86 of the 92 patients (93%), the event information was obtained from review of both the study chart and the Health Events questionnaire. For the remaining 6 patients (7%), information was obtained from the study chart review only. Medical records were obtained when possible (93% obtained). Very strong agreement was found between the self-reported and physician-verified information (kappa for type of event = 0.86; r for date of event = 0.98). Additionally, data from a subset of randomly selected study charts and questionnaires were independently extracted by a second coder

Table 1. Participants experiencing clinical events by 2 years after study entry

Health Event	Follow-up (mo) 0-12	13-24	Cumulative Sum	*P* Value*	Effect Size† *(r)*	Confidence Interval Around *r*-Effect Size
Prostate cancer treatment				.005	0.255	0.053 to 0.437
Experimental	0	2	2			
Control	6	7	13			
Radical prostatectomy				.058	0.198	−0.007 to 0.387
Experimental	0	0	0			
Control	3	2	5			
Radiotherapy				.034	0.222	0.018 to 0.408
Experimental	0	1	1			
Control	3	5	8			
Androgen deprivation				1.000	0.000	−0.205 to 0.205
Experimental	0	1	1			
Control	1	1	2			
Chemotherapy				1.000	0.000	−0.205 to 0.205
Experimental	0	0	0			
Control	0	0	0			
Other events				0.393	−0.090	−0.289 to 0.117
Experimental	13	5	18			
Control	12	4	16			
Prostate (noncancer) events				1.000	0.000	−0.205 to 0.205
Experimental	1	0	1			
Control	0	2	2			
Cardiac events				1.000	0.000	−0.205 to 0.205
Experimental	3	2	5			
Control	5	1	6			
Other cancer events				0.336	−0.101	−0.300 to 0.106
Experimental	2	1	3			
Control	1	0	1			
All other events				0.488	−0.080	−0.288 to 0.128
Experimental	11	3	14			
Control	9	3	12			

Event data available for 43 experimental and 49 control patients.
* Significance levels tested using Fisher's exact test.
† Negative effect size indicates data in opposite direction from predicted; some patients had >1 event: 2 control patients underwent both androgen deprivation and radiotherapy; 1 control patient had events in both "prostate (noncancer) events" and "all other events" categories; 3 experimental patients had events in both "cardiac events" and "other cancer events" categories; 3 intervention patients and 2 control patients had events in both "cardiac events" and "all other events" categories; and 1 control patient had events in both "other cancers" and "all other events" categories.

who was unaware of the study conditions, with good reliability found between the coders (kappa = 0.77).

As shown in Table 1, by 2 years, more control group patients (n = 13) than experimental group patients (n = 2) had undergone conventional prostate cancer treatment (Fisher's exact test, $P < .05$). Specifically, radiotherapy (8 controls and 1 experimental patient) and radical prostatectomy (5 control and 0 experimental patients) were more common among control patients than for the experimental group ($P < .01$). No significant differences were found between the groups for other clinical events. The pathology reports for the 5 control patients who underwent radical prostatectomy revealed that 3 had undergone simultaneous lymph node dissection. No lymph node metastases were noted. Stage pT3a disease was noted in 1 patient and pT2 in the remaining 4. Of these 5 patients, 2 had Gleason score 3+3 disease, 2 had Gleason score 4+3, and 1 had Gleason score 3+4 disease. With respect to the reasons for undergoing treatment, of the 13 control patients, 4 underwent treatment because of an increase in the PSA level, 4 because of an increase in the PSA level coupled with unfavorable biopsy results, and 5 because of prostate cancer progression as assessed by magnetic resonance imaging compared with earlier findings. Of the 2 experimental patients, 1 underwent treatment because of an increase in the PSA level and 1 because of cancer-related anxiety.

Additional Variables

Patients who underwent conventional treatment provided blood samples every 3 months until undergoing treatment, except for 2 control patients who missed 1 blood draw shortly before receiving treatment. The PSA velocity could not be calculated for 3 control patients who had had only 1 PSA measurement before undergoing treatment. An examination of the pretreatment PSA values showed that 3 of the 13 control patients had ≥1 PSA level that was >10 ng/mL in the period before treatment. The 2 experimental patients had a PSA level that remained at <9 ng/mL. Similarly, 1 control patient had a PSA velocity >2 ng/mL/y before treatment, and the 2 experimental patients had a PSA velocity of <1.8 ng/mL/y.

For the untreated patients, the PSA velocities could not be calculated for 3 experimental patients who had had only 1 PSA measurement, and the PSA change scores could not be calculated for an additional 5 patients (2 experimental and 3 controls) who did not provide the 24-month blood samples. The changes in PSA values in the experimental group (increase of 0.88 ± 1.88 ng/mL; PSA velocity of 0.58 ng/mL/y) did not significantly differ from those of the control group (increase of 0.99 ± 2.09 ng/mL; PSA velocity of 0.50 ng/mL/y; $P > .05$). The free PSA ratio changed from 0.14 ± 0.07 to 0.15 ± 0.08 in the experimental group and remained the same (0.15 ± 0.05 at both points) in the control group (P = NS).

Of the 36 untreated controls and the 42 untreated experimental patients, 28 (78%) and 31 (74%) completed the quality-of-life and adherence test battery. When comparing the untreated experimental and control patients for quality-of-life outcomes, no significant group-by-time interactions were found. With regard to lifestyle adherence, the average adherence for the experimental group had increased significantly from baseline (47%) to 1 year (108%) and remained high at the 2-year point (95%). In the control group, the lifestyle behaviors remained the same at all study points.

Plasma lipid and lipoprotein data were available for 37 of the 44 (84%) experimental group patients and 38 of the 49 (78%) control group patients. The experimental group patients had significant reductions from baseline to 2 years in total cholesterol (from 202.1 ± 40 mg/dL to 181.9 ± 32 mg/dL), low-density lipoprotein cholesterol (from 128.0 ± 33 mg/dL to 114.5 ± 28 mg/dL), and high-density lipoprotein cholesterol (from 46.6 ± 10 mg/dL to 42.8 ± 14 mg/dL). However, no statistically significant changes were observed in the control group. No significant effects were found on triglycerides or the total cholesterol-to-high-density lipoprotein cholesterol ratio.

COMMENT

The purpose of this study was to assess the clinical events in the PCLT at 2 years after study entry. At 1 year, 0 experimental patients and 6 control patients had undergone conventional prostate cancer therapy.[11] The present analyses revealed that this group difference in treatment was still maintained (if not enhanced) at the 2-year mark. Specifically, significantly fewer men in the experimental group had undergone conventional prostate cancer treatment (eg, radical prostatectomy, radiotherapy, or androgen deprivation therapy) compared with the usual-care control group. No significant group differences were found in the number of patients experiencing other clinical events. Although previous research focusing on biomarkers of prostate cancer has shown the benefits of this lifestyle intervention at the end of 1 year,[11,13] the results of this study have extended those findings to show that measurable benefits, in the form of fewer prostate cancer-related clinical events, were evident 2 years after study entry.

No significant difference was found in the average change in PSA values between the untreated experimental patients and the untreated control patients at the 2-year follow-up period. This null finding might be directly related to our primary finding that control patients were more likely to undergo conventional treatment. Because the purpose of the PSA analysis was to examine the effect of lifestyle changes on the natural course of cancer growth, patients who underwent conventional treatment were, necessarily, excluded from the PSA analysis. Given that an increasing PSA level often contributed to the decision to undergo treatment, these treated (and excluded) men might have been more likely to have relatively high PSA values at 2 years. It is possible that a group difference might have been observed if the data on the natural course of PSA values had been available for all patients.

The observed group difference in the incidence of treatment might not necessarily imply a group difference in cancer progression. The decision to pursue treatment is influenced by multiple factors, in addition to disease progression, including the patient's anxiety level and the opinions of the patient's family and physicians.[19,20] Because the decision to undergo treatment is influenced by many factors, one might argue that the experimental patients might have been withholding treatment even though their disease was progressing, perhaps because participating in a lifestyle program reduced their disease-specific anxiety, because of a personal commitment to continuing with the lifestyle program, or because of demand characteristics (eg, not wanting to disappoint the study staff). Although this is a viable concern, it is unlikely that the experimental patients were unsafely delaying treatment, because the experimental patients who remained treatment free were no different from their control counterparts in PSA velocity, changes in PSA, free PSA, or emotional variables. Also, the 2 experimental patients who did undergo treatment did so before their PSA level had reached 10 ng/mL and before their PSA velocity had reached 2 ng/mL/yr. In contrast, 23% of the treated control patients waited until after their PSA level was >10 ng/mL and 8% of treated control patients waited until after their PSA velocity was >2 ng/mL/y (a PSA value of >10 ng/mL and a PSA velocity of >2 ng/mL/y have been shown to be clinically meaningful cutoff points in disease severity/risk[21,22]). These observations—plus that 1 of the experimental patients (but none of the control patients) chose to undergo treatment for anxiety-related reasons—could even suggest that the decision to undergo treatment might have been more aggressive (eg, they were quicker to treat) in the experimental group than in the control group. Although it would have been ideal if additional measures of disease progression had been collected (eg, biopsy findings for all patients), there appears to be no definitive consensus as to what constitutes cancer progression in patients choosing active surveillance.[23-25]

Regardless of the reasons for the observed findings, it should be emphasized that all patients in this study had opted for active surveillance before study entry and thus desired to delay treatment and its associated harmful effects on quality of life.[2,26] Patients in the experimental group were more likely to have met this goal than the patients in the control group. In addition to the quality-of-life detriments for the patient, the economic burden for the healthcare system of treating prostate cancer with conventional methods is considerable. Recent estimates for prostate cancer costs during the first 6 months of treatment include a $12 184 cost for radical prostatectomy and ≤$24 204 for radiotherapy and $8760 for androgen deprivation. In contrast, active surveillance is estimated at $2586.[27]

Finally, the experimental patients had greater improvements in cardiovascular health parameters than did control patients, as shown by lowered total and low-density lipoprotein cholesterol levels, which might translate into a reduction in cardiac events over the long term. This is especially important because, in general, men with prostate cancer are more likely to die of cardiovascular disease than of prostate cancer.[28]

CONCLUSIONS

The results of our study have shown that participating in an intensive lifestyle program might allow patients choosing active surveillance to delay conventional treatment. Because prostate cancer is often associated with a variable or prolonged natural history, longer follow-up is necessary to determine whether the apparent benefits of the lifestyle change program are maintained beyond 24 months and whether such an approach is safe with regard to cancer control.

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