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An Integrative Approach to Prostate Cancer

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Abstract

Objectives: The mostly indolent natural history and long overall survival associated with a diagnosis of prostate cancer provides a unique opportunity for men to explore diet and lifestyle interventions to alter the trajectory of their disease. As many patients may be appropriate for postponing conventional therapy, the effects of various integrative interventions can be investigated. In addition, treatment of prostate cancer with surgery, radiation, or androgen deprivation therapy, all may produce physical or psychological side effects that could be amenable to complementary therapies. This article serves to review salient information in the published literature.

Design: A review of published research was conducted.

Results: A plant-based antioxidant-rich diet with an emphasis on cruciferous vegetables, tomatoes, soy, pomegranate, and marine omega 3 fatty acids while avoiding saturated fats, including dairy products is the best option. Supplementation with vitamin D3, omega 3, and some nutraceutical-based preparations may be advised. It is likely prudent to avoid vitamin E and selenium supplements. Physical activity has been shown to have multiple benefits in men diagnosed with all stages of prostate cancer from strengthening bones, improving body habitus, and enhancing overall wellbeing. Yoga, combining physical activity with a mind–body component, has been shown to have a salutogenic effect in both prostate cancer patients and their caregivers. Traditional Chinese Medicine may be particularly useful in managing side effects of conventional treatments, especially the hot flashes associated with androgen deprivation therapy. Although the long natural history, availability of a useful blood marker of disease progression and prolonged survival are overall positive features, they also combine to allow men to live for a long time with diagnosed cancer, fear of progression, or recurrence and fixation on changes in their prostate-specific antigen level. The resultant stress can be deleterious to general health as well as possibly the natural history of their disease. Mind–body interventions to reduce stress, including mindfulness-based stress reduction and support groups may be useful adjunctive therapies.

Conclusion: Men with prostate cancer may benefit from lifestyle and complementary interventions integrated with their conventional care.

Keywords: prostate cancer, integrative, nutrition, supplements, exercise, acupuncture

Introduction

Prostate cancer is the most frequently diagnosed malignancy in men accounting for 19% of all male cancers. It is estimated that 164,690 new cases will be diagnosed in the United States in 2018.[1–3] Approximately 11.6% of all men will be diagnosed with prostate cancer during their lifetime. The incidence of prostate cancer is markedly higher in African Americans. Prostate cancer is most frequently diagnosed in men 65–74 years of age with a median age at diagnosis of 66. The percent of prostate cancer deaths is highest among men 75 to 84 with a median age at death of 80. With an estimated 29,430 deaths from prostate cancer in 2018, it will rank as the sixth leading cause of cancer deaths.

The 5-year survival rate with prostate cancer is 98.6% based on SEER data from 2007 to 2013, making it one of the less virulent malignancies. This finding, in fact, has led many, including the U.S. Preventive Services Task Force, to suggest that screening a large number of men with the readily available prostate-specific antigen (PSA) test should be discouraged as it leads to overdiagnosis and overtreatment and may not significantly impact survival.[4] A sharp decline in new cases diagnosed was noted in 2010 to 2014 reflecting the 2008 recommendation not to screen men over 75, and the 2011 recommendation not to screen at all.[5] A

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Table 1. Impact of Nutritional and Lifestyle Changes in Prostate Cancer

Intervention	*Effects*	*Refs.*
Nutritional		
Maintain a normal body–mass index	↓ risk for recurrence	11,12
Decrease animal fats (except fish), including dairy	↓ risk	15–17,19
Increase lycopene-rich foods	↓ risk; unclear in established cancer	16,20–23
High cruciferous vegetable intake	↓ risk, recurrence, aggressive disease, possible slow PSA doubling time	24–27
Increase whole soy foods	↓ risk; unclear effect in established cancer	20,28
Drink green tea	↓ risk; unclear effect in established cancer	
Dietary supplements		
Nonherbal supplements		
Supplement with vitamin D3 as needed	Best to avoid deficiency or excess after diagnosis, low levels ↑ risk of metastasis	20,37–39
Avoid vitamin E, selenium, and supplemental calcium	↑ risk	16,20,32–36,42
Omega 3 fatty acids	↓ risk Supplementation with low fat diet improves *in vitro* parameters with established cancer	17,45
Herbal supplements		
Modified citrus pectin	Preliminary suggestion of prolonged PSA doubling time and more stable disease	46
Zyflamend™	May reverse premalignant conditions	20,47
Pomegranate or Pomi-T®	May slow PSA doubling time	20,31,48
Lifestyle changes		
Physical exercise	↓ risk improve outcome with established cancer ↑muscle mass and strength	49 50 51,52
Yoga	↓ fatigue and sexual dysfunction	53
Additional CIM modalities		
Acupuncture/Traditional Chinese medicine	↓ chemotherapy-induced nausea and vomiting ↓ hot flashes	55 56,57
Reiki	Improved emotional wellbeing	58
Mind–body therapies, including mindfulness-based stress reduction	↓ stress and anxiety	59,60

CIM, complementary and integrative medicine; PSA, prostate-specific antigen.

possible increase in late-stage disease in men 50–64 years of age prompted the Task Force to recommend informed decision making in the 55–69-year-old age group.[6]

Many of the unique features of prostate cancer make it a malignancy particularly suitable for integrative medicine interventions. The availability of a blood-screening test has generally allowed for the majority of men to be diagnosed with localized disease. The ability to prognosticate outcomes from PSA levels and the prostate pathology has led to an increasing number of men choosing to postpone conventional surgery or radiation therapy in favor of active surveillance.[7,8] This period of what is no longer referred to as ''watchful waiting'' as it was deemed too passive provides a window of opportunity to incorporate lifestyle changes that may further delay the need for conventional intervention as well as improving the individual's overall wellbeing.

Similarly, the generous lifespan after a confirmed diagnosis followed by treatment also allows for the possibility of lifestyle interventions that may further improve both quality and quantity of life. The long survival after diagnosis has challenges as well as men often make their cancer the center of their life activity and concern and become very fixated on any changes in their PSA values or minor symptomatology, fearing disease recurrence or spread. These individuals may particularly benefit from some of the mind–body-based interventions that integrative medicine has to offer. Patients with advanced disease may suffer symptoms from the cancer itself or its treatment that may also be amenable to integrative interventions.

Nutrition

Weight

The Centers for Disease Control estimates that overweight and obesity accounted for 40% of all cancers diagnosed in 2014.[9] Although prostate cancer is not among the 13 cancers associated with excess body weight in the CDC list, there is evidence that obesity is associated with more aggressive prostate cancer.[10] Fat increases cancer risk through a number of mechanisms. Fat produces inflammatory cytokines. Inflammation impairs immunity and the body's tumor surveillance system. Excess body fat also leads to insulin resistance with increased levels of insulin and insulin-like growth factor, both of which stimulate prostate cancer growth. A meta-analysis involving 26,479 men in 26 studies found that overweight and obesity are responsible for 12%–20% of prostate cancer deaths.[11] For

every 5 kg/m^2 increase in body–mass index (BMI), there was a 21% increased risk of biochemical recurrence and a 15% increased risk of death from prostate cancer.

A correlation between consumption of energy-dense foods and an increased risk of highly aggressive prostate cancer has also been noted.[12] A study of intentional weight loss before prostatectomy in men with prostate cancer yielded mixed effects on circulating biomarkers, tumor gene expression, and proliferative markers.[13] In any event, overweight and obese men with prostate cancer should be advised to lower their BMI to less than 25 to at least decrease the risk of developing other weight-related malignancies in addition to possibly impacting on their known tumor's progression (Table 1).

Diet

Navigating the current cancer diet craze maze can be overwhelming for the man with prostate cancer. Should he follow the Alkaline, Budwig, Ketogenic, Macrobiotic, or Paleo eating plan? Or perhaps fast altogether! In general, an organic, plant-based, antioxidant-rich, anti-inflammatory whole foods diet is perhaps the best recommendation.[14] Plant-based seems recommended in view of the fact that studies have suggested positive associations between prostate cancer and animal fat (total and saturated), red meat, milk and dairy products, and energy from alcohol and sugar, although the American Institute for Cancer Research/World Cancer Research Fund finds the meat and dairy evidence to be limited.[15,16] Fish appears to protect against prostate cancer as well as cancer at other sites likely through its anti-inflammatory omega 3 fatty acids, so a strict vegetarian or vegan diet is not mandated.[17] Eggs had also been implicated in increasing prostate cancer risk,[18] but recent analyses suggest that there is not a strong association.[17,19]

Among the plants most recognized to have an impact on prostate cancer are tomatoes, rich in lycopene, a potent antioxidant carotenoid also found in other red fruits and vegetables, such as watermelon and pink grapefruit.[16] Lycopene in tomato is best absorbed if fat soluble, hence cooked in olive oil as tomato sauce or paste. Studies confirm that lycopene may inhibit growth and metastasis of prostate cancer cells *in vitro* and animal models.[20] Epidemiological studies have demonstrated that populations with high dietary lycopene intake have lower risks of prostate cancer.[20] Intervention studies investigating a lycopene diet or tomato-based food products in men with various stages of premalignant prostate changes (high-grade prostate intraepithelial neoplasia [HGPIN]), established localized or metastatic disease are difficult to conduct and yield inconsistent results.[20] It is easier to conduct trials with a pharmaceuticalized lycopene supplement, but these as well have yielded conflicting conclusions.[21–23]

Greater consumption of cruciferous vegetables is associated with a lower risk of developing aggressive prostate cancer.[24,25] Isothiocyanates and indoles derived from the hydrolysis of cruciferous glucosinolates, such as sulforaphane and indole-3-carbinol, have been implicated in a variety of anticarcinogenic mechanisms. A study demonstrated that men with localized prostate cancer consuming a half cup of cruciferous vegetables daily had a lower risk of recurrence compared with men who ate none.[26] Another trial investigated a sulforaphane supplement to slow PSA velocity in men with recurrent PSA elevation following surgery or radiation with less than stellar results.[27]

Epidemiologic studies confirm that Asian men are at lower risk of developing prostate cancer. It is suggested that soy intake is inversely associated with risk and may protect against the development of prostate cancer. A meta-analysis of studies that investigated soy food consumption suggested that high consumption of nonfermented soy foods (e.g., tofu and soy milk) may significantly decrease the risk of prostate cancer; however, no effect was seen for fermented soy foods (miso).[28] Soy isoflavones are phytoestrogens. *In vitro*, the isoflavone genistein affects multiple growth and proliferation-related pathways in prostate cancer cells, with the combined effect of multiple isoflavones being greater than that of a single one.[29] Although a few studies in patients with established prostate cancer appreciated some positive impact of drinking a prescribed number of glasses of soy milk for a prolonged study period, most trials have investigated isolated soy isoflavones with inconsistent results.[20]

Another reason that Asian men may have lower rates of prostate cancer is the high intake of green tea polyphenols that have also been demonstrated to have significant *in vitro* activity against prostate cancer cell lines.[20] A meta-analysis examining the consumption of green and black tea found a statistically significant inverse association between green tea consumption in three case–control studies but not in four cohort studies.[30] No association was found for black tea. Although some clinical trials have sought to investigate the effect of tea drinking on progression in patients with established prostate cancer, most have investigated green tea extract capsules or supplements containing the most potent polyphenol, epigallocathechin-3-gallate (EGCG), with inconsistent results.[20]

Polyphenolic compounds in the pomegranate when applied as a juice or extract inhibit the proliferation of prostate cancer cell lines *in vitro*, inducing apoptosis in a dose-dependent fashion.[20] After rodent studies confirmed that pomegranate juice decreased the rate of development, growth and spread of prostate cancer, a human trial was conducted.[31] Forty-eight men with PSA recurrence following treatment drank 8 ounces of pomegranate juice for up to 33 months. PSA doubling time rose from a mean of 15 months to a mean of 54 months ($p < 0.001$). In view of the sugar content of drinking 8 ounces of juice daily and its potential overall unhealthy effect, as well as the American Institute for Cancer Research/World Cancer Research Fund admonition to ''avoid sugary drinks,'' pomegranate may be one food item that could perhaps be best taken as a dietary supplement rather than as a juice product.

Supplements

Many of the food components mentioned above have been assayed as dietary supplements in prostate cancer clinical trials.[20] In most instances, the whole food product is preferred, except perhaps as mentioned for pomegranate juice. There are, however, some dietary supplements that may be worth considering, used to decrease the risk or improve the outcome in men with established prostate cancer. The potential of supplements to decrease the risk of prostate cancer was dealt with a significant blow with the results

of the Selenium and Vitamin E Cancer Prevention Trial (SELECT) study.[32] Where the early trial of β-carotene and vitamin E to decrease the risk of lung cancer failed to demonstrate a benefit, there was a suggestion of a decrease in the rate of prostate cancer in men who had been randomized to vitamin E.[33] Selenium, an essential trace mineral important for a number of biological processes, had also been identified in animal and epidemiological studies as having a protective effect against developing prostate cancer.[20] Hence, the SELECT study was initiated to examine the effect of either or both on the development of prostate cancer.[34] The large multicenter trial that enrolled more than 35,000 men beginning in 2001 was terminated early in 2009 when it became apparent that the trial would not reach a positive endpoint. Later analysis after longer follow-up revealed that the men randomized to receive vitamin E actually had a 17% increase in the risk of developing prostate cancer ($p=0.008$).[35] Selenium supplementation had no overall effect on prostate cancer risk in men with low selenium levels at baseline, but increased the risk of high-grade prostate cancer by 91% in men with higher baseline selenium status ($p=0.007$).[36]

Low levels of vitamin D have been associated with an increased risk of a number of malignancies, and in patients with various types of cancer, low vitamin D levels are often associated with worse outcomes. The situation with prostate cancer is less clear cut. A meta-analysis of 21 studies, including 11,941 cases and 13,870 controls, suggested a 17% increased risk of developing prostate cancer in men with higher levels of 25-hydroxyvitamin D [25(OH)D].[37] On the other hand, the situation in men with established prostate cancer is different. Epidemiological studies have suggested that patients with the lowest levels of vitamin D have the greatest risk of developing metastatic disease while those with higher levels have a better prognosis.[38] An interesting observation was made regarding seasonal variation of PSA elevation.[39] With vitamin D generated by exposure to sunlight, it was observed that PSA levels increase slower during the spring and summer possibly reflecting higher serum levels of 25(OH)D.

As there appears to be a U-shaped curve for outcome and mortality with serum 25(OH)D levels,[36] it would seem prudent to aim for patients to achieve a reasonable 25(OH)D level in the 40–50 ng/mL range, avoiding either under- or oversupplementation with a gel bead or liquid vitamin D3 (cholecalciferol) preparation. The hormonally active form of vitamin D3—calcitriol—has been investigated as a possible therapeutic intervention in men with prostate cancer. In one open-label, phase II trial, calcitriol plus naproxen appeared to be effective in slowing PSA[40] rise, whereas a later study in castrate-resistant patients evaluating calcitriol and dexamethasone showed no effect on PSA levels.[41]

Vitamin D is involved in calcium absorption and homeostasis. The role of calcium in prostate cancer etiology has been investigated in numerous epidemiological studies which in turn, have been subjected to meta-analyses.[20] The major sources of calcium intake in the United States are dairy products and dietary supplements. There has long been a concern that dairy products may be linked to prostate cancer causation.[20] The evidence has been contradictory in numerous studies.[20] The American Institute for Cancer Research/World Cancer Research Fund 2007 report concluded that there was probable evidence that diets high in calcium intake increased the risk of prostate cancer,, but only limited evidence implicating milk and dairy products.[16]

A more recent meta-analysis, however, concluded that high intake of dairy products (milk, low-fat milk, cheese), total dietary calcium intake, and dairy calcium may increase prostate cancer risk.[42] Nondairy calcium and supplemental calcium were not associated with an increased risk, although calcium supplements did appear to increase the risk of fatal prostate cancer. As calcium appears to be protective for the development of colorectal cancer and bone density loss, it may be prudent for men with established prostate cancer who chose to eliminate dairy from the diet to supplement with a low daily dose (300–500 mg) of calcium.

Omega 3 fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—are found primarily in fish and shellfish. Epidemiological studies suggest that consumption of fish rich in omega 3 fatty acids may reduce the risk of prostate cancer.[17] Obfuscating this observation, however, was a finding from the SELECT study that men with the highest blood levels of omega-3 fatty acids had a 43% increased risk of developing prostate cancer, and a 71% higher chance of developing high-grade prostate cancer.[43] Men were advised to avoid fish oil supplements. Concerns were raised about the interpretation of these observational findings.[44] This was a secondary analysis and not one of the primary endpoints of the original trial. No information was collected on participants' use of fish oil supplements so the elevated levels obtained from a single blood test do not suggest causation.

Perhaps a more enlightening study was a randomized prospective controlled trial of supplementation with omega 3 fatty acids in men about to undergo prostatectomy.[45] In this trial, men with prostate cancer were randomized to a low-fat (15% calories from fat) diet and 4 g of omega 3 supplements daily for 4 to 6 weeks before prostatectomy. The control group consumed the standard American diet with 40% of calories from fat and no fish oil supplementation. At prostatectomy, the experimental group had smaller prostates (both benign and malignant components), lower proliferation index, and plasma that inhibited growth of prostate cancer cells *in vitro* more than the plasma from the control patients.

Hence, it seems safe and prudent to recommend fish oil supplementation in men with prostate cancer. Four grams may be a high dose especially if surgery is planned as this level of supplementation may impair clotting so, as a rule, patients may want to eliminate omega 3 supplements in the perioperative period. Vegetarians should be apprised that the main omega 3 fatty acid found in plants—α linolenic acid—is not the same as DHA and EPA and information on its effect in prostate cancer is lacking.

Many of the foods mentioned as protective or beneficial in preventing prostate cancer or demonstrating *in vitro* evidence against cultured prostate cancer cells have been made available as dietary supplements. Patients may find these supplements particularly appealing, especially if they have a distaste for the natural food product. Pomegranate may be the best to consider as a supplemental capsule as it is a fruit that is not readily available, is difficult to consume, and the recommended delivery system–juice—is loaded with sugars.

A study of 200 μg of sulfurophane from cruciferous vegetables was conducted in men with PSA recurrence following surgery or radiation.[27] There was some evidence that sulfurophane might be useful in prolonging PSA doubling time. Until more conclusive evidence is obtained, eating broccoli seems like a better way of obtaining the potential benefit and is in keeping with the World Cancer Research Fund/American Institute for Cancer Research guideline to meet nutritional needs through diet alone and not to use dietary supplements for cancer prevention.[16]

Modified citrus pectin is another supplement made from citrus fruit peels that have been altered to increase bioavailability. A recent preliminary publication from an ongoing trial in 34 patients with PSA recurrence suggests that modified citrus pectin may be a useful supplement.[46] In the planned early analysis, 62% had stabilization or decrease in PSA and negative scans at 6 months and 79% had increased PSA doubling time. This uncontrolled trial will increase enrollment to 60 participants and follow patients for a more prolonged time, but many men have already added modified citrus pectin to their regimen of supplements.

There are also nutrient-based supplement combinations that have been studied in men with, or at risk for, prostate cancer. Zyflamend™ is a botanical with anti-inflammatory activity that has been demonstrated to significantly inhibit human prostate cancer cells in culture.[20] The supplement contains extracts of rosemary, turmeric, ginger, holy basil, green tea, Hu zhang, Chinese goldthread, barberry, oregano, and Baikal skullcap. In the lone phase I study published to date, men with HGPIN, a premalignant condition, were treated with Zyflamend three times a day for 18 months while receiving additional supplements as well.[47] At the end of the study period, participants underwent repeat biopsy, at which time 60% had only benign tissue, 27% had HGPIN, and 13% had progressed to prostate cancer. The supplement was well tolerated in the phase I trial with the main side effect being dyspepsia that improves when taken with food.

Pomi-T®, composed of powders of pomegranate, broccoli, and turmeric with green tea extract, was evaluated in a randomized, double-blind, placebo-controlled trial of 199 men with localized prostate cancer.[48] Study participants were on active surveillance (60%) or had rising PSA levels following local therapy. After 6 months, the Pomi-T®, recipients had sustained a median rise in PSA of 14.7% compared with 78.5% in the placebo group. Treatment was well tolerated overall with the main side effects being increased flatulence and loose bowels in the treatment group. Other proprietary combination supplements marketed to men with prostate cancer have not yet been subjected to rigorous clinical evaluation.

Lifestyle

Physical activity, both job related and recreational, has been inconsistently associated with a decreased risk of developing prostate cancer. It appears as if physical activity itself might slightly lower the risk, but regular vigorous activity in men younger than 65 appears to lower the risk and especially that of developing more aggressive disease.[49]

In men with an established prostate cancer diagnosis, regular physical activity has been associated with improved outcomes. The relationship between postdiagnosis physical activity and mortality was evaluated in 2705 men in the Health Professionals Follow-Up Study diagnosed with nonmetastatic prostate cancer and observed from 1990 to 2008.[50] Among men surviving at least 4 years after their physical activity assessment, those who were physically active had lower risk of all-cause mortality ($p_{trend} < 0.001$) and prostate cancer mortality ($p_{trend} = 0.04$). Nonvigorous and vigorous activities were both beneficial. Men who walked 90 min or more weekly at a normal to very brisk pace had a 46% lower risk of all-cause mortality (hazard ratio [HR] 0.54; confidence interval [95% CI] 0.41–0.71) compared with shorter durations at an easy walking pace. Men with ≥3 h per week of vigorous activity had a 49% lower risk of all-cause mortality (HR 0.51; 95% CI 0.36–0.72) and a 61% lower risk of death from prostate cancer (HR 0.39; 95% CI 0.18–0.84; $p = 0.03$) compared with men reporting less than 1 h per week.

Another reason men with prostate cancer should have a regular program of physical activity is to preserve bone density, especially while receiving androgen deprivation therapy. A pilot study in Korea randomized 51 men with prostate cancer on androgen deprivation therapy to a 6-month, home-based exercise program aimed at decreasing the risk of osteoporosis ($N = 26$) or a stretching exercise control group ($N = 25$).[51] The primary endpoints were bone density and markers of bone turnover. Eighty percent of the patients were retained at 6 months. Although no differences were noted between groups in the primary bone-related endpoints, participants in the home-based exercise program for preventing osteoporosis had more muscle strength than the stretching control group.

Physical activity is usually not strongly recommended in men with osseous metastases from prostate cancer for fear that it may lead to pathologic fractures. An Australian study randomized 57 men with bone metastases from prostate cancer to a supervised multimodal program involving aerobic, resistance and flexibility exercises three times a week for 3 months or to a no exercise control group.[52] Significant differences between the groups were noted for self-reported physical functioning and objective measures of lower body muscle strength favoring the exercise group. No differences were appreciated between groups for lean body mass, fat mass, or fatigue. No adverse events related to exercise or fractures were noted in the experimental group. There was no difference noted in bone pain reported between the two groups.

Yoga is a physical activity that promotes strength, balance, and flexibility while providing mind–body benefits as well. When one is moving with the breath and assuming the yoga postures, other thoughts and stressors are put on the back burner. Men diagnosed with prostate cancer are frequently at an age where strength, balance, and flexibility need attention. Living with a cancer diagnosis, no matter how indolent one is told the disease may be, is a major source of stress. Thus, yoga appears to be a physical, mental, and spiritual exercise that may be particularly beneficial.

One study randomized men with prostate cancer undergoing radiation therapy to yoga classes twice a week during the 6 to 9 weeks of radiation therapy or to a no yoga control group.[53] In the end, 22 patients in the yoga group and 28 in the control group were evaluable. Throughout treatment, those in the yoga arm reported less fatigue than those in the

control arm as well as improvement in sexual health scores as measured by the International Index of Erectile Function Questionnaire. The effects on urinary symptoms and quality of life measures were less consistent with the yoga intervention.

Another feasibility study investigated the impact of yoga on 15 prostate cancer survivors and 10 of their support persons.[54] Participants received a total of seven 75-min yoga classes once a week over the 7-week study period. The trial was designed more as a feasibility study, but did collect outcome measures, including use of thermometer ratings for acute changes between before and after class as well as a battery of standardized tools. Comparisons of the thermometer ratings from before to after each class revealed improvements in prostate cancer survivors' mood ($p=0.000$) and decreases in levels of fatigue ($p=0.000$) and stress ($p=0.004$). Similar benefits were reported by the support persons. However, over the entire 14-week study period, no significant persistent changes in fatigue or quality of life parameters were noted in either the patients or their support persons. The authors recognized that the small sample size and lack of a control group may have impacted their results.

Complementary Therapies

Hot flashes are a common adverse effect of androgen deprivation therapy in men undergoing treatment for prostate cancer. Acupuncture is one of the main treatment modalities of the system of Traditional Chinese Medicine. The goal of acupuncture is to restore energy balance in the body by guiding the flow with needles strategically placed in acupoints along the body's meridians. Some practitioners find referral to a Traditional Chinese Medicine practitioner for diagnosis and treatment to be especially useful in conditions for which standard Western interventions may fall short. A National Institutes of Health consensus conference in 1997 concluded that acupuncture was effective in treatment of chemotherapy-induced nausea and vomiting.[55]

Two small clinical trials have investigated acupuncture as a treatment for hot flashes secondary to androgen deprivation therapy. In the first, 22 men with hot flash scores greater than 4 were enrolled in a trial of acupuncture through electrical stimulation.[56] Participants received treatment twice weekly for 4 weeks, then weekly for 6 weeks using a predefined treatment plan. After 4 weeks, nine (41%) of the patients reported a greater than 50% reduction in their hot flash scores, which also translated into an improvement in their hot flash-related quality of life and sleep quality. No patient experienced an increase in hot flashes during this uncontrolled trial. In a second uncontrolled study, 14 patients with at least three hot flashes a day received acupuncture from the same experienced practitioner twice a week for 4 weeks.[57] Participants reported improvements in their hot flash scores at 2 and 6 weeks and even at a time point 8 months after enrollment. No adverse effects were recorded.

Reiki is an energy therapy used to enhance the body's ability to heal itself. A feasibility study was conducted to assess whether men undergoing radiation therapy for prostate cancer would participate in a trial that randomized them to various complementary therapies concurrent with their conventional treatment.[58] Participants were randomized to standard of care, Reiki therapy, or relaxation response therapy (RRT) with cognitive restructuring. RRT teaches patients to evoke the relaxation response, which assists in replacing negative thoughts with less frightening and more positive images (cognitive restructuring). Reiki sessions were given twice weekly during the 8 weeks of radiation and RRT was once a week. There were 18 participants randomized to each of the three groups demonstrating the feasibility of patients accepting randomization to complementary therapies. Although the study was too small to be powered for effectiveness endpoints, the investigators found significant improvement in the emotional wellbeing subscale of the FACT-G quality-of-life scale in the RRT group compared with the other two. In patients classified as anxious at baseline, improvements were seen in both the RRT and Reiki study participants.

Mind/Body

Mindfulness-based stress reduction (MBSR) is a program that incorporates relaxation, meditation, and yoga taught over an 8-week course with encouragement to develop and continue a daily home practice. An early study included 49 women with breast cancer and 10 men with prostate cancer.[59] The study collected information on quality-of-life measurements as well as physiological parameters, including cortisol levels, proinflammatory cytokines, and blood pressure, and provided follow-up at 6 and 12-month time points. The investigators found improvements in overall symptoms of stress that were maintained over the entire duration of follow-up. In addition, they reported declines in cortisol levels, proinflammatory cytokines, and systolic blood pressure, all correlating with decreased stress and improved quality of life.

Mindfulness stresses increased awareness of the present and encourages the person to become less avoidant and less reactive to their experience. The practice aims to reduce identification with thoughts and trains participants in equanimity. This ultimately serves to enable them to be more accepting as well as aware of negative emotions and challenging situations.

Men with early stage prostate cancer undergoing active surveillance were randomized to either an 8-week MBSR training ($n=24$) or an attention control arm ($n=19$) in a pilot study.[60] Participants completed self-reported measures of prostate cancer anxiety, uncertainty intolerance, global quality of life, mindfulness, and posttraumatic growth at baseline, 8 weeks, 6 months, and 12 months. In this small feasibility study, mindfulness was found to be feasible and acceptable to the patients with 47% of the men approached electing to participate. Participants in the mindfulness arm demonstrated significant decreases in prostate cancer anxiety and uncertainty intolerance as well as significant increases in mindfulness, global mental health, and posttraumatic growth. Of note, the control group only experienced a significant increase in mindfulness over time. With regard to within-group differences, longitudinal increases in posttraumatic growth were significantly greater in the treatment group than the control group.

Putting It All Together

Meditation and support group participation were two key features of the lifestyle modification regimen offered to

participants in the comprehensive integrative regimen followed in the ''Ornish regimen.''[61] As opposed to studying the effect of a single phytonutrient or exercise modality on a narrowly defined endpoint, the Ornish protocol offered patients a truly integrative intervention that combined diet, exercise, and stress reduction. The randomized, controlled trial was open to men with low or favorable intermediate-risk prostate cancer choosing not to undergo conventional therapy. Men in the experimental group were prescribed a vegan diet with $\sim$10% of calories derived from fat. The diet was supplemented with soy, fish oil (3 g daily), vitamin E (400 IU daily), selenium (200 mcg daily), and vitamin C (2 g daily). Participants were instructed to walk 30 min 6 days a week. Stress management techniques included gentle yoga-based stretching, breathing, meditation, imagery, and progressive relaxation for 60 min daily. In addition, the men participated in a support group for 1 h weekly to enhance adherence to the study intervention. Control patients were not asked to make diet and lifestyle changes although some did so to varying degrees.

After the first 12 months of follow-up, six of the control patients had elected to undergo conventional treatment, whereas none in the experimental group sought surgery or radiation. PSA levels dropped to an average of 4% in the lifestyle change group and rose 6% in the control subjects ($p=0.016$). The extent to which patients altered their lifestyle was found to be significantly correlated with their degree of PSA drop. By 2 years of follow-up, 13 of 49 (27%) of the control patients and 2 of 43 (5%) of the experimental patients had been treated with conventional interventions for their prostate cancer ($p<0.05$).[62]

Over time, the experimental cohort demonstrated significant improvements in weight, abdominal obesity, blood pressure, and lipid profiles.[63] Genetic profiling revealed that the experimental group modulated expression of genes that play a critical role in tumorigenesis. The comprehensive lifestyle intervention was also found to be associated with increases in relative telomere length compared with the control condition after 5 years of follow-up in a small subset of the larger cohort.[64] This elegant translational work reinforces the concept that integrative interventions may have profound biological impact in men living with prostate cancer that could significantly alter the course of disease and hopefully lead to improvements in both quantity and quality of life.

Conclusion

As the Ornish study demonstrates, the optimal integrative approach to prostate cancer is a multipronged combination of a number of lifestyle interventions and complementary therapies and not just a single modality (see Table 1). Adopting an organic, plant-based, antioxidant-rich, anti-inflammatory, whole foods diet rich in phytonutrients, including lycopene, soy isoflavones, and polyphenolic compounds, such as those in green tea and pomegranate, while reducing saturated fats, is recommended. In conjunction with a vigorous program of physical activity, dietary changes may facilitate the maintenance of a healthy body weight. Yoga is both a physical activity as well as a mind–body intervention that may aid in reducing the stress that accompanies a cancer diagnosis. Traditional Chinese Medicine, especially acupuncture, may be of value in reducing symptoms associated with advanced prostate cancer or its treatment. In total, an integrative approach to prostate cancer may be best for enhancing both the quality and duration of life.

Author Disclosure Statement

No competing financial interests exist.

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