

Diet and Survival After Prostate Cancer Diagnosis

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Prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States. Among environmental factors, diet may play a particularly important role in its incidence, progression, and clinical outcome. This article reviews the findings of eight observational studies and 17 intervention or laboratory trials on the effect of plant-based diets and plant nutrients on both the progression and clinical outcome of prostate cancer as well as additional studies examining mechanisms that may explain dietary effects. While additional long-term therapeutic clinical trials are needed to further elucidate the role of diet, these early investigations suggest that a recommendation for individual patients to shift their diets toward plant foods may serve as an important component of the tertiary treatment of prostate cancer.

Key words: diet, prostate cancer, prostate, cancer prognosis, survival, recurrence, mortality

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INTRODUCTION

In the United States, prostate cancer is the most commonly diagnosed non-skin cancer and the second leading cause of cancer-related death in men after lung cancer.^{1,2} Evidence suggests that environmental factors, particularly diet, may play a role in prostate cancer incidence and mortality. Comparison of age-standardized incidence rates shows dramatic international variation in

risk of prostate cancer. For example, the rate in Qidong, China, is only 0.5 per 100,000 men, compared with 111.2/100,000 for Caucasian men in Atlanta, Ga, USA, and 142.3 per 100,000 for African-American men in Atlanta, Ga, USA (relative risk 222.4 and 284.6, respectively).²

Significant increases in prostate cancer risk have been observed in Asian and other low-risk populations upon migration to the United States.^{3–6} Prostate cancer rates in Japanese men increase 4–9-fold within the first generation and by the second generation the rates approximate those of the US-born population.⁴ Similarly, the incidence of prostate cancer is significantly lower in Western Africa than in the United States, yet African Americans who trace their origins to this region experience a 50% higher incidence of prostate cancer than white Americans.⁷ Recently, Sim and Cheng⁸ attributed the observed 5–118% rise in the incidence of prostate cancer in various Asian countries between 1978 and 1997 to the gradual Westernization of the diet.

Epidemiologic studies have indicated significant associations between specific foods and nutrients and prostate cancer risk. In large population studies performed in over 60 countries,^{9,11,14} as well as in prospective cohort studies,^{10,12,14} intake of dairy products,^{13,14} red meat,^{12,13} and total dietary fat,^{9,10,11} have been found to be positively correlated with increased risk of prostate cancer. In contrast, consumption of soy products,^{11,15} fiber-containing foods,^{11,16} cruciferous vegetables,^{17,18} and lycopene^{19,20} has been reported to be inversely associated with prostate cancer risk. Diet may also play a role in the course of the disease after diagnosis. Investigators have assessed the effect of diet on indices of prostate cancer progression, as well as on clinical outcome, in epidemiologic, laboratory, and intervention studies. This review reports on the findings published to date and suggests dietary approaches for potential improvement in prostate cancer prognosis and survival.

LITERATURE REVIEW

A MEDLINE (National Library of Medicine, Bethesda, Md, USA) search was conducted for studies

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published on the relationship between prostate cancer survival and diet using the following key words: diet, prostate cancer, prostate, cancer, prognosis, survival, recurrence, and mortality. The studies included in the review were limited to human studies published in the English language for the period catalogued since 1966. The bibliographies of articles were searched for additional relevant articles. All reports that met the criteria of directly addressing the relationship between diet and prostate cancer survival were included. This search yielded eight observational studies and 17 intervention or laboratory studies.

OBSERVATIONAL STUDIES

Two observational studies examined the associations between dietary factors assessed shortly after diagnosis and death from prostate cancer.^{21,22} One study prospectively examined the relative risk between diet and fatal prostate cancer.²³ Three studies examined associations between overall dietary intake and progression of cancer,^{14,24,25} one examined trends between adolescent dietary intake and subsequent adult disease risk,²⁶ and another examined the effect of self-selected macrobiotic diets on survival and disease status.²⁷ Table 1 summarizes the findings of these observational studies.

Meyer et al.²¹ and Bairati et al.²⁴ reported on the relationship between dietary fat intake, as assessed using questionnaires for food frequency and diet history at the time of diagnosis, on cancer progression and 5-year prostate cancer survival in a group of men in the Quebec City area of Quebec, Canada. After controlling for grade, clinical stage, initial treatment, age, and total energy intake, men with higher percentages of energy intake from saturated fat were observed to have an increased risk of death from prostate cancer, compared with those with lower intakes.²¹ Among men with the highest intake of saturated fat, the risk of dying from prostate cancer was three times higher than that of men with the lowest intake (>13.2% vs <10.8%) of total energy. Bairati et al.,²⁴ using participants with local disease to serve as the comparison group for those with advanced disease for all analyses, reported that saturated fat intake was also found to be the dietary component most strongly associated with prostate cancer progression. Inverse associations were observed between the finding of advanced cancer at the time of diagnosis and polyunsaturated fat and linoleic acid intake. Similar findings were reported in a population-based case-control study performed in the US state of Utah.²⁵ In that study, the reference period for dietary intake history was 3 years prior to diagnosis. The most significant association between dietary intake and tumor aggressiveness, as defined by tumor grade and stage, was observed for dietary fat. A positive association with prostate cancer progression and total and satu-

rated fat and an inverse association with mono and unsaturated fat have been observed in many^{9,21,23,30} but not all³¹⁻³³ studies. The cause for inconsistencies in the findings among these reports is not clear. However, they may reflect non-respondent bias or difficulty in recall; they may also be the result of overly brief questionnaires.²³ For example, the findings of no association between high-fat²⁶ or vegetarian³⁴ diets in early childhood with the risk of metastatic prostate cancer in adulthood may have been artifactual, resulting from reliance on inaccurate recall of diet in the distant past.

In order to determine the relationship between pre-diagnostic diet and prostate cancer survival, researchers looked at structured diet-history questionnaires encompassing 200 food items consumed during the 12-month period prior to diagnosis from men newly diagnosed with prostate cancer from Vancouver and Toronto, Canada.²² Following adjustments for clinical stage, histologic grade, and demographic factors, higher total pre-diagnostic energy intakes were associated with a lower risk of death from prostate cancer over 7 years of follow-up. Significantly lower risks of dying from prostate cancer were observed in the men in the highest compared to the lowest tertile of monounsaturated fat intake. Association of risk of death from prostate cancer and vegetable fat intake followed the same pattern as risk of death from prostate cancer and monounsaturated fat intake. These associations parallel those reported for diet and risk of progression of prostate cancer.^{24,25}

Chan et al.¹⁴ examined post-diagnostic consumption of red meat, grains, vegetables, fruits, milk, tomatoes, tomato sauce, and fish in subjects from the Health Professionals Follow-up Study. Increasing the post-diagnostic consumption of tomato sauce by two servings per week resulted in an inverse linear relation with the risk of progression. A similarly increased consumption of fish also resulted in decreased risk of progression. Increasing consumption of either fish or tomato sauce by one serving per day was associated with an approximate 50% lower risk of progression, independent of pre-diagnostic diet or other post-diagnostic foods. The apparent effect of fish intake on decreased risk of progression is unclear; however, it may be due, in part, to the omega-3 fats, docosahexaenoic acid, and eicosapentaenoic acid content of fish.

Carter et al.²⁷ compared nine men with metastatic (stage D2) prostate cancer who opted for a macrobiotic diet after prostate cancer diagnosis with nine men who did not alter their diets. The subjects were matched according to age, Gleason score, and treatment. The macrobiotic diet (10–12% fat), as modified for cancer patients, was composed of 50–60% whole cereal grains, 25% vegetables, 15% beans and sea vegetables, and 5% miso soup. Mean length of survival was 177 months (median 228 months) for patients who adopted a macro-

Table 1. Summary of Observational Studies of Prostate Cancer (PC) Survival and Diet

Reference	No. of subjects (age)	Study design	Length of time	Results
Chan (2006) ¹⁴	329 (40–75 y)	Prospective study examining post-diagnostic diet and risk of PC progression	12 y	Inverse relationship with increasing post-diagnostic consumption of tomato sauce and risk of progression of PC, HR=0.56 (0.38–0.82); men in highest vs. lowest quartile of consumption had a 40% reduced risk of progression HR=0.73 (0.52–1.02)
Meyer (1999) ²¹	384 (≥45 y)	Prospective study of association between dietary fat intake and PC survival	5 y	Saturated fat consumption was associated with disease-specific survival (2-sided, <i>P</i> =0.008). Risk of dying from PC was 3 times greater in upper-intake tercile vs. lower-intake tercile RR=3.1 (1.3–7.7)
Kim (2000) ²²	263 cases (63.3–76.6 y)	Prospective study of association of prediagnostic energy, fat and vitamin A intake, and survival from PC	4–6 y	Lower risk of death associated with lowest tertile of monounsaturated fat intake HR=0.3 (0.1–0.7) (<i>P</i> trend=0.01). Highest tertile of energy intake associated with lowest risk of death HR=0.1 (0.01–0.6). Vitamin A intake not associated with risk of death
Hsing (1990) ²³	17,633 (≥35 y)	Prospective study associating diet and risk of fatal PC	20 y	No dietary factors associated with fatal PC
Baitati (1998) ²⁴	384 (≥45 y)	Retrospective case study evaluating influence of diet on advanced PC	Within 1 y diagnosis	Highest quartile of fat intake vs. lowest TO=2.15 (1.14–4.04). Proportional increase with saturated fat intake TO=1.24 (1.02–1.51). Inverse association between advanced PC and PUFA TO=0.88 (0.73–1.07). Positive trend for total animal fat intake TO=1.20 (0.99–1.46). Negative trend for total vegetable fat intake TO=0.84 (0.70–1.01)
West (1991) ²⁵	356 cases (45–74 y), 679 controls	Population-based case-control study to investigate association of dietary energy, fat, protein, vitamin A, β-carotene, vitamin C, zinc, cadmium, and selenium with PC	3-y period prior to diagnosis	In older males (68–74 y) dietary total fat had the strongest association with aggressive tumors OR=2.9 (1.0–8.4); followed by saturated fat OR=2.2 (0.7–6.6), monounsaturated fat OR=3.6 (1.3–9.7), and polyunsaturated fat OR=2.7(1.1–6.8). Other dietary constituents had little or no association
Slattery (1990) ²⁶	362 cases (45–75 y), 685 controls (<65 y)	Case-control study assessing reported food consumption patterns as adolescents and adults on risk of developing metastatic PC as adults	Cases identified within 6 w of diagnosis	Elevated risk of developing aggressive tumors associated with high saturated fat diet as adults OR=1.8 (1.0–3.2). No association observed with adolescent diet
Carter (1993) ²⁷	9 cases (46–88 y), 9 controls (46–88 y)	Retrospective case-controlled study examining effect of consumption of a very low-fat, high-fiber, low-energy “macrobiotic” diet on survival after PC diagnosis	1 y	Mean length of survival time = 177 months (cases) vs. 91 months (controls); OR=1.6 (–2.39–3.33) (Woolf) ≥2 mg lutein plus zeaxanthin vs. <0.8 mg OR=0.68 (0.45–1.00)

Abbreviations: RR, relative risk (95%CI); TO, trend odds ratio (95%CI); OR odds ratio (95%CI); HR, hazard ratio (95%CI)

Table 2. Summary of Intervention Studies on Prostate Cancer Survival and Diet

Reference	No. of subjects (age)	Design/intervention	Length of time	Results
Tymchuk et al. (2002) ³⁶	Intervention: 8 (54±4 y); control: 14 (60.±3 y)	Nonrandomized clinical trial: consumption of plant-based, low-fat, high-fiber diet plus exercise on serum-stimulated growth of established PC cell lines	Mean 14.2 y (range, 6–20 y)	LNCaP cell growth in subject serum was 40% lower than fetal bovine serum-stimulated serum ^{**} and 49% lower than that of controls. ^{**} Neither testosterone nor estradiol stimulated PC-3 cells in subjects compared to controls, but they increased LNCaP cell growth by 12% ^{**} and 16% ^{**} , respectively
Omish et al. (2005) ³⁷	Intervention: 44 (65±7 y); control: 49 (67±8 y)	Randomized clinical trial: effect of low-fat vegan diet with SR [†] support on changes on PSA in untreated PC patients	1 y	PSA decreased by 4% in the experimental group and increased by 6% in the control group ($P=0.016$). Growth of LNCaP cells was inhibited 60% more by serum from the intervention group compared to the control group ^{***}
Saxe et al. (2001) ³⁸	10 (61–78 y)	Nonrandomized clinical trial: effect of SR [†] along with a plant-based, low-saturated fat, high-fiber diet on rate of change in PSA in men with recurrent PC	4 mo	Rate of rise in PSA decreased in 8 subjects ($P=0.01$) and the estimated median doubling time increased from 6.5 to 17.7 months (95%CI, 3.7 to 10.1); (95%CI, 7.8 to ∞), respectively
Saxe et al. (2006) ³⁹	14 (61–78 y)	Nonrandomized clinical trial: effect of SR [†] along with a plant-based, low-saturated fat, high-fiber diet rate of change in PSA in men with recurrent PC	6 mo	Rate of rise of PSA was less during intervention compared to prior to study. ^{**} Median PSA doubling time increased from 11.9 mo (pre-study) to 112.3 mo (intervention)
Spentzos (2003) ⁴⁰	2-step intervention: 18 (71 y)	Step 1: low fat 15% of calories; step 2: low fat + soy protein + antioxidants	Median, 10.5 mo	Median PSA _{dT} = 11.3 mo; median prolongation = 5 mo vs. baseline ($P=0.06$); median TTP = 6.63 mo vs 3.0 mo free testosterone (median, -5% $P<0.01$); mean increase in IGFBP-3 ^{**} -3of10% ($P=0.02$)
Tymchuk et al. (2001) ⁴¹	Intervention: 13 (59±4 y); patient control: 4 (61–80 y); control for bioassay: 7 (38–80 y)	Nonrandomized clinical trial: effect of consumption of plant-based, low-fat, high-fiber diet plus exercise on serum-stimulated growth of established PC cell lines	11 d vs. 14.2 y	LNCaP cell growth in serum from men after an 11-d intervention was reduced by 30% compared to preintervention. ^{**} LNCaP cell growth in serum from men on regimen for 14.2 y was 15% less than that of 11 d post-intervention serum. ^{**} Decrease in LNCaP growth did not correlate significantly with reduction in free testosterone

Table 2. (Cont'd)

Reference	No. of subjects (age)	Design/intervention	Length of time	Results
Aronson et al. (2001) ⁴⁸	Intervention: 9 (64–83 y)	Nonrandomized clinical trial: low-fat, fish oil-supplemented diet fed to men with untreated PC	3 mo	There was an increase in omega-3/omega-6 fatty acid ratios in plasma ($P=0.002$) and gluteal tissue ($P=0.002$), but not in adipose tissue. COX-2 expression in prostatic tissue decreased in 4 patients
Demark-Wahnefried et al. (2001) ⁴⁹	Intervention: 25 (63.3±8.0 y); control: 25 (64.1±7.0 y)	Randomized clinical trial: low-fat, flax seed-supplemented diet fed to PC patients awaiting prostatectomy matched with historical controls	34±13 d (21–77 d)	Total testosterone*, serum cholesterol* and free androgen* were less in treated subjects compared to controls. There were no differences in PSA at follow-up, but both the proliferation rate ($P=0.049$) and apoptosis ($P=0.017$) were associated with number of days on the diet
Demark-Wahnefried et al. (2004) ⁵⁰	Intervention: 15 (61.5±11.2 y)	Nonrandomized clinical trial: low-fat, flax seed-supplemented diet fed to PC patients to examine effect on benign epithelium	6 mo	Reductions in PSA ($P=0.0002$) and cholesterol ($P=0.0120$) were observed at follow-up, as compared to baseline. Proliferation rates in benign epithelium decreased at 6 months.** There were no differences in total testosterone
Kucuk et al. (2002) ⁵⁸	Intervention: 15 (62.3±1.9 y); control: 11 (62.0±1.8 y)	Randomized clinical trial: 30 mg/day lycopene as extract consumed by patients with localized PC	3 wk	At 3 weeks, mean PSA levels decreased by 18% in the intervention group compared to an increase of 14% in controls ($P=0.22$). Tumors were smaller (80% vs 45%) ($P=0.22$) and plasma levels of IGF-1 ^{††} decreased ($P=0.0003$) in treatment vs control groups. Plasma IGFBP ^s decreased in intervention ($P=0.002$) and control ($P=0.0001$) groups
Chen et al. (2001) ⁵⁹	30 (63.7±6.1 y)	Nonrandomized clinical trial: 30 mg lycopene/day consumed in tomato sauce-based pasta dishes by patients with localized PC	3 wk	After intervention, serum and prostate lycopene concentrations were higher.*** Leukocyte oxidative DNA damage ($P=0.005$), tissue oxidative damage ($P=0.03$), and serum PSA levels*** were reduced

Table 2. (Cont'd)

Reference	No. of subjects (age)	Design/intervention	Length of time	Results
Heinonen et al. (1998) ⁶⁵	α -tocopherol: 14,456; control: 14569; β -carotene: 14,560; control: 14573	Randomized controlled trial: effect of α -tocopherol and β -carotene supplementation either separately or together on male smokers	6.1 y (range, 5–8 y)	A 32% decrease in the incidence of PC (95%CI –47% to –12%) and 41% lower mortality (95%CI –65% to –1%) was found among those receiving α -tocopherol compared to controls. PC incidence was 23% higher (95%CI –4% to –59%), mortality was 15% higher (95%CI –30% to –89%) among those receiving β -carotene supplementation compared to controls. Among subjects receiving both supplements, incidence of PC and mortality was 16% lower and mortality approximately 40% lower than controls
Urban et al. (2001) ⁶⁸	Intervention: 17/17 (65.3 \pm 2.3 y)	Randomized double-blind crossover trial: effects of consumption of soy protein beverage (ISP) on men with elevated PSA on PC biomarkers	6 wk/6 wk	No decreases in serum biomarkers PSA or p105erbB-2 were observed
Hussain et al. (2003) ⁷¹	41 (55–82 y)	Nonrandomized clinical trial: soy isoflavone given to PC patients either 1) newly diagnosed with rising PSA, 2) with increasing PSA following local therapy, or 3) receiving hormone therapy	5.5 mo (0.8–6 mo)	Stabilization of PSA occurred in 83% of patients in group II and in 35% of those in group III. Rate of rise of PSA decreased in all groups ($P=0.01$). No significant change in serum levels of testosterone, IGF-1 [†] , IGFBP-3 [§] , or 5-OHmdU
Jarred et al. (2002) ⁷²	Intervention: 18 (60.5 \pm 6.6 y); control: 18 (60 \pm 5.3 y)	Nonrandomized clinical trial: effect of red clover-derived dietary isoflavones given to patients with nonmetastatic PC	20 d (range, 7–54 d)	Incidence of apoptosis was greater in treatment group compared to controls ($P=0.0018$). No significant difference in pre- and post-treatment serum PSA, testosterone, or Gleason score
deVere et al. (2004) ⁷³	62 (61.4–89.3 y)	Nonrandomized clinical trial: effect of soy isoflavon (genistein-rich extract) on PSA levels	6 mo	A genistein-rich extract as sole treatment for PC did not reduce PSA levels by $\geq 50\%$ in 51/52 subjects

Table 2. (Cont'd)

Reference	No. of subjects (age)	Design/intervention	Length of time	Results
Schroder et al. (2005) ⁷⁵	Radical prostatectomy: 34 (69.8±7.1 y); radiotherapy: 15 (69.8±7.1 y)	Randomized double-blind crossover trial: effect of consumption of soy-based dietary supplement on rate of increase of PSA	10 wk/10 wk	PSA doubling time increased 2.6× ($P=0.030$). PSA slope per protocol decreased 2 log PSA ($P=0.030$) and slope of the 2 log serum total PSA decreased ($P=0.041$)
Kranse et al. (2005) ⁷⁶	Intervention: 19/18 (na)	Randomized double-blind crossover trial: effect of consumption of isoflavone and carotinoïd-based beverage (verum) along with margarine on rate of increase of PSA	6 wk/6 wk	Male sex hormone levels were lower ($p=0.005$) and free PSA decreased ($P=0.02$) during verum phase compared to placebo. In men in whom androgen index decreased (21/32), slopes of total and free PSA also decreased ($P=0.04$). PSA doubling time was unaffected

* $P<0.05$

** $P<0.01$

*** $P<0.001$

[†]Stress reduction

^{††}Insulin-like growth facotor-1

[§]Insulin-like growth factor binding protein

^{||}Oxidative stress marker

biotic diet, compared with a mean length of survival of 91 months (median 72 months) for controls. Although the contribution of individual food groups or nutrients to overall length of survival was not examined, possible mechanisms are the combined antineoplastic effects of the individual food components such as antioxidants,¹⁷ glucosinolates,²⁸ plant lignans,²⁹ and fiber,^{35,36} as well as reduced calories,³⁷ for inhibiting tumor development.

In summary, results from eight observational studies suggest that tumor aggressiveness and death from prostate cancer may be directly associated with dietary total fat and saturated fat intake, while polyunsaturated and monounsaturated fat intake may have no association or be inversely associated with tumor aggressiveness and death from prostate cancer. Consumption of individual foods such as tomato sauce, in addition to a specific combination of foods as prescribed in a macrobiotic diet, may also improve mean survival time.

DIET INTERVENTION TRIALS

Three clinical intervention trials have examined the effect of a plant-based diet along with stress reduction and/or exercise on markers of prostate cancer progression.³⁷⁻³⁹ A summary of the results of these and other intervention trials is presented in Table 2. In two separate studies of recurrent prostate cancer (rising prostate-specific antigen [PSA] after prostatectomy), both of which had each patient serving as their own control, Saxe et al.^{38,39} reported a significant decrease in the rate of PSA increase in men consuming a plant-based diet combined with stress reduction for periods of 4³⁸ and 6³⁹ months following prostatectomy. In the later study,³⁹ the median PSA doubling time increased from 11.9 months prior to the intervention to 112.3 months by the end of 6 months. Further, four of the patients experienced an absolute reduction in their PSA levels, an effect usually only observed in this patient subpopulation after administration of hormonal therapy. In a similar 1-year dietary and lifestyle intervention trial of newly diagnosed prostate cancer patients undergoing watchful waiting, PSA levels in the intervention group also decreased significantly compared to the control group.³⁷ In addition, in this study, serum was taken from both groups and administered separately to cultured LNCaP cells. Serum from the experimental group inhibited LNCaP growth 8 times more than serum from the control group. Six control group patients required treatment during the study due to progression of prostate cancer while, in contrast, no experimental group patient required treatment.

Low-fat, high-fiber diets, particularly vegetarian diets, are typically associated with decreased plasma concentrations of sex hormones.^{35,40} As prostatic activity is dependent on testosterone, prolactin, and estrogen, dietary interventions that modify circulating concentrations of these

hormones may be expected to influence risk and progression of prostate cancer. Two other *in vitro* studies evaluated the effect of consumption of a low-fat, (10% of calories from fat) high-fiber diet, together with exercise, on serum-stimulated growth of established prostate cancer cell lines.^{36,41} In the earlier study,⁴¹ serum was collected from two groups of men: 13 who followed the regimen for 11 days and eight who followed it for 14.2 years. Serum concentration of free testosterone fell by an average of 17% in the 11-day participants. In both groups, LNCaP growth measured in post-intervention serum was significantly lower compared to growth in pre-intervention serum. There was no difference in the growth of PC-3 cells in either group.

In the later study,³⁶ serum from eight men who had adhered to the program for a mean of 14.2 years was used as a growth medium for LNCaP cells with the addition of testosterone, estradiol, and/or insulin. Compared to cells grown in fetal bovine serum and control groups, the cells grown in serum from the intervention group showed 40% and 49% less growth, respectively. Addition of testosterone, estradiol, and insulin to serum from the intervention group significantly stimulated LNCaP cell growth *in vitro* but accounted for only about half of the difference between the control and the diet group, suggesting that other serum hormones, growth factors, or binding proteins may play a role in the observed serum effect in diet-and-exercise subjects.^{42,43}

These studies suggest that changes in diet and lifestyle, including increased fiber and decreased fat intake along with increased exercise and stress management, may serve as an adjunct to conventional therapy. However, it is unclear how stress reduction and/or exercise, *per se*, or providing the patient an active role in his care, independent of dietary intervention, affect outcome. Some studies have been limited by small sample size or by lack of randomization.^{36,41} Extrapolation of *in vitro* results to *in vivo* applications should be made with caution. However, diet-induced hormonal modulation may explain, in part, the epidemiological observations^{21,22,24,27} and findings that plant-based, low-fat, high-fiber diets may influence prostate cancer growth and progression.

Other intervention studies have evaluated the contribution of specific dietary components as well as food to tumor progression and death from prostate cancer, in the absence of lifestyle changes.

TRIALS ASSESSING DIET COMPONENTS WITH POSTULATED EFFECTS ON CANCER PROGRESSION

Low-fat, high-fiber diets

Specific fatty acids, in particular, omega-3 and omega-6 fatty acids, have been reported to influence prostate cancer growth. Some authors have suggested that a high

dietary ratio of omega-3:omega-6 fatty acids may influence growth signal factors by inhibiting the enzymes that are active in the synthesis of eicosanoids, which play a role in cancer initiation and proliferation.^{44,45} Omega-6 fatty acids may exert a stimulatory effect on the growth of PC-3 cells by enhancing the proliferation of malignant prostate epithelial cells, thereby increasing the risk of advanced prostate cancer.^{44,45,47} In several short-term intervention trials, the low-fat diets of cancer patients were supplemented with omega-3 fatty acids.⁴⁸⁻⁵⁰ In the first two trials, patients were supplemented with flaxseed for respective periods of 1 month and 6 months.^{49,50} After 34 days, PSA levels were lower, while apoptotic indices, serum cholesterol, total testosterone, and free androgen were significantly lower compared to baseline. After 6 months of treatment, PSA levels were significantly lower, compared to pre-trial levels, as were mean proliferation rates of benign prostatic epithelium. There was also a positive association between serum PSA levels and the rate of cell proliferation, suggesting that the effect of a low-fat, plant-based diet, which is high in phytoestrogens, on slowing progression of prostate cancer may be dose dependent. Accordingly, in this study, androgen levels were lowered, possibly due to the dose level and/or fat restriction of the diet, in addition to flaxseed, as compared to other studies.^{51,52} Cholesterol levels also decreased in both studies. Cholesterol may be indirectly linked to prostate cancer in that it provides the sterol ring structure for testosterone. Diets high in fiber have also been associated with decreases in estradiol and testosterone.³⁵ This is probably related to fiber's ability to bind sex hormones as they undergo enterohepatic circulation, thereby reducing circulating cancer cell growth promoters.⁵³ Although testosterone levels decreased significantly in the 1-month study, this was not the case in the longer study. The lack of power may explain these results.

In the third trial, patients were supplemented with fish oil for 3 months.⁴⁸ The COX-2 m-RNA expression in prostate tissue decreased in 57% of the patients, and the omega-3:omega-6 fatty acid ratio in plasma and gluteal tissue increased significantly compared to baseline. Increased expression of COX-2 has been demonstrated in prostate cancer compared to benign tissue,^{54,55} suggesting a lessening in disease markers. These studies were limited by having few subjects, difficulty in sampling, and short duration. The potential for a low-fat diet high in omega-3 fatty acids to prevent development and progression of prostate cancer, requires examination.

Components of Fruits and Vegetables

Non-fiber components of fruits and vegetables may also confer protection against prostate cancer progression. For example, *Brassica* vegetables have been re-

ported to have chemopreventive properties such as inducing apoptosis and inhibiting prostate cancer cell proliferation in vitro,⁵⁶ reducing tumor invasion and metastasis, as well as affecting other complex cellular interactions.⁵⁷ Xiao et al.⁵⁶ examined androgen-dependent and androgen-independent cultured prostate cells exposed to isolated allyl isothiocyanate (AITC), a component of cruciferous (*Brassica*) vegetables. In vitro, AITC was found to suppress growth of both types of cells equally, while minimally affecting survival of the normal prostate epithelial line. Epidemiological^{16,57} and case-control¹⁷ evidence modestly supports these in vitro and clinical findings. Cruciferous vegetables appear to be protective in prostate carcinogenesis, possibly due to their high levels of isothiocyanate sulforaphane, a potent inducer of glutathione *S*-transferase, a phase II enzyme-inducing agent.¹⁸

Lycopene is a carotenoid found in tomato products, watermelon, pink grapefruit, and other fruits. Two 3-week intervention studies using either a lycopene supplement (30 mg/day) in newly diagnosed prostate cancer patients⁵⁸ or tomato sauce-based dishes (providing 30 mg of lycopene/day) in patients with localized prostate adenocarcinoma,⁵⁹ found that mean serum PSA levels decreased along with cytological markers (smaller tumors, less involvement of margins and/or extrahepatic tissue) indicating decreased prostatic activity following the interventions. Lycopene has also been shown to inhibit the growth of human cancer cells in tissue culture.⁶⁰ An up-regulation of Cx43 along with a down-regulation of IGF-1 in patients with localized prostate cancer may contribute to decreased growth and induced apoptosis in malignant prostate cells.^{61,62} Some,^{19,20,62} but not all,^{17,34} epidemiological and case-control studies suggest an inverse association exists between lycopene intake and prostate cancer risk. These inconsistent findings may be due to study designs that do not control for total vegetable consumption, participants' bias, and accuracy of questionnaires.

Long-term daily supplementation with 50 mg alpha-tocopherol in Finnish smokers was associated with a substantial reduction in the incidence of and mortality from clinically overt prostate cancer but did not have an effect on advanced prostate cancer.⁶⁵ It is possible that alpha-tocopherol influenced the transformation of latent cancers to clinical cancers. Vitamin E may protect against cancer by enhancing immune function and preventing the propagation of free radical damage in biological membranes.⁶⁶ Prostate cancer incidence was 23% higher and mortality was 15% higher among men who received beta carotene than those who did not. Some case-control studies support these findings^{30,39} while other large chemopreventive trials⁶⁷ and some case-control studies have found no association or even protection.³³

Soy

Some authors have hypothesized that the lower prostate cancer mortality rate among Japanese men, compared to men from the United States, may be partly attributable to their high level of soy protein intake.^{30,69} In general, Asian men have a lower incidence of prostate cancer than men in the United States.^{2,3} However, although the incidence of latent prostate cancer is comparable in Asian and Western countries, prostate cancer-specific mortality is much higher in the West. This observation has led to the study of dietary factors that differ between Asian and Western populations. One such factor is soy intake.⁷⁰ In an uncontrolled study to determine the effect of soy isoflavone supplementation (100 mg twice daily) on prostate cancer markers, patients with prostate cancer were grouped according to whether they had newly diagnosed and untreated disease (group I), had increasing PSA levels following local therapy (group II), or were receiving hormone therapy (group III).⁷¹ In all three groups, the rate of PSA level elevation decreased compared to baseline rates, although there were no sustained decreases in PSA levels. Other researchers have reported similar findings.^{40,72,73}

Soy isoflavones may be associated with slowing of prostate cancer progression, as reflected in a decrease in the rate of PSA elevation, as a result of their binding to estrogen and androgen receptors.⁷⁴ This process may be mediated through a specific effect of genistein on PSA protein synthesis and secretion.^{19,74} Despite significant increases in the serum isoflavones genistein and daidzein, no significant changes were observed in any of the groups' serum concentrations of insulin-like growth factor-1, insulin-like growth factor binding protein-3, testosterone, or 5-hydroxy-methyl-deoxyuridine. Similarly, in post-surgical patients, deVere et al.⁷³ observed no difference in the pre- and post-surgery levels of PSA or testosterone in men with nonmetastatic prostate cancer. Following surgery, however, apoptosis in prostate tumor cells was observed more frequently in specimens from treated participants than in those from control participants, specifically in regions of low- to moderate-grade cancer. These findings suggest that dietary isoflavones may also play a role in inducing apoptosis, especially in low- to moderate-grade tumors. In contrast, other authors have reported that the inhibition of enzymes associated with cancer cell growth and signal transduction *in vitro* may be modulated by the down-regulation of insulin-like growth factor-1, leading to inhibition of growth, prevention of oxidative DNA damage, and modulation of estrogenic or antiestrogenic effects.^{40,70}

Several randomized studies have examined the effect of the consumption of soy in combination with other

nutrients, on markers of prostate cancer progression.^{46,49,71,75,76} In one study, patients consumed a supplement consisting of soy isoflavones, lycopene, silymarin, and antioxidants after prostatectomy or radiotherapy to assess the effect of the supplement on the rate of increase of PSA.⁷⁵ A significant decrease in PSA slope and ²log PSA slope was observed at the end of the treatment period. In one small study, men scheduled to undergo radical prostatectomy were randomized to diets supplemented with soy, soy and linseed, or wheat.⁷⁷ After the intervention, there was a significant difference in the percentage of change in total PSA and the free:total PSA ratio between those men consuming both of the soy supplements compared to those consuming wheat. There were no differences between the two groups consuming soy. These results are in agreement with the results of Denmark-Wahnefried et al. and Hussain et al.^{50,71} and may be related to the estrogenic effect of isoflavones on peripheral testosterone synthesis. Phytoestrogens block the activity of the enzyme that converts androstenedione to testosterone, thus inhibiting prostate cancer cell growth by either slowing down cell proliferation⁷⁴ and/or increasing apoptosis.⁷² It is uncertain if these findings translate into a slowing of disease progression. Larger randomized controlled trials are needed to support these findings.

In a similar study, men with confirmed rising PSA levels (>0.1 ng/ml) consumed a dietary supplement containing soy along with lycopene and antioxidants.⁷⁶ In contrast, at the end of this trial, total PSA and total PSA doubling time were unaffected, although free PSA, dihydroxytestosterone, and testosterone levels decreased significantly. The lack of effect on PSA may be due, in part, to the heterogeneity of the beginning PSA levels of study participants and the short intervention period.

Another non-randomized clinical trial tested the effects of a low-fat diet or a low-fat diet with the addition of a soy supplement on PSA progression in patients having undergone radiation or surgery.⁴⁰ Both diets derived 15% of calories from fat and included daily supplements of 400 IU vitamin E, 200 ug selenium, and a multivitamin. A significant decrease in free testosterone, which was consistent with the previous,⁷⁶ but not all,^{72,74} observations, was reported during the low-fat plus soy supplement phase. PSA did not decline by $\geq 50\%$ from baseline in either group; however, the PSA mean doubling time and estimated time-to-progression were modestly longer during the low-fat-plus-soy supplement phase and the low-fat phase alone, respectively. These differences may be explained by the fact that although there was a decrease in free testosterone levels in some studies, which is possibly reflective of estrogenic or antiestrogenic effects,^{40,41} in other studies, free testosterone may not have been sufficiently depressed to affect

clinical progression. The addition of coenzyme Q10 along with a similar soy supplement had no effect on serum levels of PSA.⁴⁶ A recommendation to consume soy products, either alone or in combination with certain nutrients, may be useful for adjunctive treatment of prostate cancer, particularly in the early stages of the disease.

CONCLUSION

Overall, the preponderance of available evidence (i.e., eight observational studies and 17 clinical or laboratory trials) suggests that short-term dietary modifications may be associated with indices of reduced disease progression.^{14,21,22,24,25,27,36-39,41,48,49,50,56,58,59,65,71-73,75-77} Two observational studies found no association,^{23,26} possibly due to limits in assessing food consumption patterns. In prospective studies of prostate cancer patients, consumption of a diet high in saturated fat is associated with about a 3-fold higher risk of progression of and death from prostate cancer compared to consumption of a diet low in saturated fat (<10% calories). Findings for vegetable fat, particularly monounsaturated fat, have been mixed. Patients who adopt a plant-based diet after disease onset or unsuccessful treatment may experience a lower rate of progression compared to those who do not. Intake of specific foods or nutrients may play a role in this process. Consumption of soy foods or soy or isoflavone supplements has been reported to improve prostate cancer prognosis.^{40,72,73} A slowing of disease progression was observed in prostate cancer patients consuming flaxseed or lycopene-containing foods or supplements.^{49,50,58,59} These studies suggest that predominantly plant-based diets that are high in fiber and phytonutrients and low in fat and saturated fat, favorably influence health outcomes for prostate cancer patients. Diet may influence circulating hormone levels and modulate androgenic or estrogenic effects, resulting in inhibition of cancer cell growth and/or increased apoptosis. While the mechanisms by which specific diet components benefit prostate cancer survival remain to be elucidated, the effects of consumption of plant-based diets on markers of prostate cancer progression observed in these studies are encouraging. Some limitations of the early research include studies with small numbers of patients, lack of randomization, difficulty assessing compliance, separating effects of lifestyle from dietary changes, as well as identifying effects of specific foods versus nutrients. Longer-term clinical trials with adequate power are needed to further determine the sustainability of these interventions and their effect on prostate cancer-specific and overall survival.

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