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Dietary Interventions in Prostate Cancer

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Abstract

Data regarding diet and prostate cancer are accumulating and randomized controlled trials are currently underway which will ultimately yield evidence on which to base recommendations regarding dietary regimens, functional foods, and supplement-use. Until then, most data derive from epidemiologic investigations that have limitations in showing cause and effect, or from bench top research which may have limited application to in vivo systems (including the human). While there is not enough evidence to support the use of any dietary supplement or functional food at this time, clinicians should encourage weight management as a top priority within their clinic practices, since data consistently show that overweight and obesity are associated with progressive disease and increased overall mortality from prostate cancer, as well as other diseases (e.g., cardiovascular disease).

Keywords

prostatic neoplasms; diet; nutrition; body weight; dietary supplements

Introduction

More than a quarter of a century ago, Doll and Peto estimated that between 10–90% of cancer mortality was due to dietary factors [1]. Previous research suggests there is good reason to suspect that the foods that we consume, in essence the substrate that we supply to our body cells, is associated with the etiology and progression of cancer [2*,3*,4–7]. For a hormonally-driven cancer, such as prostate cancer, this link may be even stronger since factors such as body weight and habitus, and intakes of fat, fiber and other dietary constituents have been found to influence androgen metabolism, as well as other metabolic pathways that have been identified as important for this disease [3*,4–7,8*]. Data from laboratory and epidemiologic studies abound and there is new information each week about promising dietary interventions [2*,3*,4–7,8*]. Today, if patients searched the web for the phrase “diet” (or nutrition) and prostate cancer,” they would be greeted with roughly a quarter of a million “hits” leading them to believe that definitive research has been conducted in this arena. However, how much do we really know? Indeed, there is some interesting nutritional research on the horizon, but will it “hold water?” Should it be recommended? And, does it have the potential of doing more harm than good? What is fact and what is hype? And how can we guide desperate cancer patients toward sound dietary practices and away from premature panacea?

The purpose of this paper is to strategically review the state of the science that currently exists regarding dietary interventions and prostate cancer. The ultimate goal is provide the clinician with some sense of assurity in delivering guidance which is likely to benefit or at least not harm the patient, and to distinguish this from nutritional interventions which require much more

study before they can be endorsed. In addition, the article provides information about reliable resources, as well as some rudimentary decision rules regarding the potential of dietary interventions to either help or hurt patients.

How Do We Know What We “Know” About Diet and Prostate Cancer?

To a large extent, our knowledge- base regarding diet and prostate cancer comes from epidemiologic investigations, and basic research conducted on cell lines and in animal models [4,5]. Such research has been instrumental in guiding advancements in therapeutics, and also has played a key role in the discovery of the impact of various lifestyle exposures (example: tobacco) on cancer risk [1]. However, these scientific approaches also have limitations. An inherent limitation of epidemiologic studies is an inability to prove cause and effect. In contrast, bench top research adeptly discerns cause and effect, but is bound by a potential inability to generalize findings to valid *in vivo* systems and ultimately to the human [9]. In the area of diet and cancer, the track record of identifying nutrients that go on to show success in clinical trials is dismal at best. Reasons for this are many and include, but are not limited, to the following: 1) dietary intake is difficult to measure; 2) nutrient composition of food is affected by growing conditions, storage and preparation; 3) databases for measuring dietary intake are incomplete; 4) food is complex and comprised of myriad nutrients and non-nutrient constituents that may share various synergic or antagonistic associations, furthermore the human diet is even more complex; thus disentangling diet-related substances that are on the causal pathway versus those that are only markers of intake is difficult; 5) animals and people have much different metabolic rates and nutrient needs and consume much different diets (as an example the usual mouse diet is roughly 4% fat - a level which is much lower than even the 20–35% level advocated within the U.S. Dietary Guidelines) [10**]; 5) the bioavailability of nutrients is affected by several factors including the specific chemical form of the nutrient, dose, timing of dose, intake of other foods at the time of ingestion, medications, stomach acidity, intestinal microflora and motility, etc.; 6) nutrient thresholds exist, therefore supplementing individuals who already consume an adequate intake may not be helpful; and 7) a host of gene-nutrient interactions exist that govern events that range from taste preferences to metabolism[4,6]. Therefore, even if the results of epidemiologic studies, and research in cell culture and animal models all appear to support various nutrients or functional foods, there still is no assurance that the same effects will borne-out in humans [11].

So, What’s the Big Deal? A Vitamin May Not Help, But It Certainly Can’t Hurt, Can It?

In one of the first maiden voyages of nutritional chemoprevention aimed at reducing lung cancer, the Alpha Tocopherol and Beta Carotene (ATBC) Trial found that beta-carotene, a food-related constituent in the same family as lycopene, was ineffective in reducing incidence amongst high risk smokers [12]. Not only was it ineffective in reducing risk, it actually increased it [12]. Investigators in the midst of the Carotene and Retinol Efficacy Trial (CARET) quickly analyzed their preliminary data and found similar results; it was one of the few dietary intervention studies to ever employ stopping rules [13]. It is worth noting that both of these trials were launched on promising data from epidemiological studies and basic science experiments; however it is clear that we did not fully understand the complexity of vitamin supplementation before launching these large, costly studies – a lesson that should be carried into the future [11]. A potential silver lining however is that although beta-carotene was found to increase risk of lung cancer in the ATBC trial, the same trial produced secondary findings which suggested that vitamin E supplementation (75 IU/day) reduced the risk of prostate cancer by 32% [12]. Data from this study were reanalyzed after 19 years of follow-up and reported this summer; while no differences were found regarding vitamin E intake and prostate cancer, significant protective associations were found between baseline serum levels of alpha tocopherol and risk of developing advanced disease (Relative Risk [R.R.] = 0.56; 95% Confidence Interval [C.I.]: 0.36–0.85), an association which was even stronger among men

who received the supplement [14]. While these findings reinforce the potentially favorable effect of vitamin E supplementation, they also may just suggest that men who were more well-nourished at time of study entry had better health outcomes. Indeed, other recent findings regarding vitamin E show less favorable results. In a recent clinical trial conducted on 540 head and neck cancer patients receiving radiotherapy and randomized to 400 IU/day of vitamin E versus placebo, significantly higher all-cause mortality (Hazards Ratio [H.R.]=1.38; 95% C.I.: 1.03–1.85), as well as increased cause-specific mortality were found in those who received vitamin E [15*]. These findings ride on the heels of a meta-analysis by Miller *et al.* [16] which showed significantly higher ($p=0.035$) all-cause mortality with 400 IU or more of vitamin E/day. Some thought leaders within the field of nutrition have speculated that single nutrient interventions may be similar to monotherapy in the treatment of cancer, and that while transformed or malignant cells might be held at bay for a brief period of time with such interventions, they are unlikely to work long term [17]. Instead, more complex cocktails of nutrients might be needed, and subsequently multivitamin preparations became viewed as “safer” options. Recent findings from two studies, however, suggest that this may not be the case, i.e., even when supplements are combined or when they are in the form of multivitamin preparations there still may be a problem [18**,19*]. In February of this year, a systematic review and meta-analysis of all randomized trials involving beta-carotene, vitamin A, vitamin C, vitamin E and selenium (a total of 68 trials with 232,606 participants) found a significantly increased risk of mortality for beta-carotene, vitamin A and vitamin E when used either alone or in combination [18**]. Later, findings from the National Institutes of Health (NIH) – American Association of Retired Persons (AARP) study ($N=295,344$) reported that multivitamin supplements were associated with increased risk of advanced [R.R.:1.32; 95% C.I.: 1.04–1.67] and fatal prostate cancer [R.R.: 1.98, 95% C.I.: 1.07–3.66] in men taking more than seven multivitamins per week [19*]. This risk appeared strongest among men with a positive family history and those who took individual micronutrient supplements in addition to multivitamins.

In view of this research, clinicians should be circumspect regarding the endorsement of any nutritional supplements unless it is under the rubric of a clinical trial. Like pharmaceutical agents (particularly when doses exceed the upper limits)[20], it also must be borne in mind that nutritional supplements may carry a host of side effects and risks that may impact patient health in more immediate ways than affecting prostate cancer progression. Dangers of overdose can be fatal are a real possibility, particularly with trace elements and various fat-soluble vitamins [21,22]. The National Institutes of Health Office of Dietary Supplements and the National Center for Alternative and Complementary Medicine (<http://ods.od.nih.gov> and <http://nccam.nih.gov>) provide reliable sources of information to both patients and providers regarding nutrient supplements, as well as functional foods and dietary regimens.

What Dietary Interventions Have Actually Been Done in Prostate Cancer – Where Are We?

As of the December 2007, there have been 37 published studies that have reported effects of dietary interventions on prostate cancer prevention and control in humans; the number of studies is increased by two if case studies are counted. Note that this does not include research regarding PC-SPES nor studies for which prostate cancer was a secondary endpoint or those aimed at endpoints which were non-prostate cancer specific, i.e., functional status, quality of life, co-morbidity, etc. (endpoints which will be addressed briefly later in this article). While the sheer number of studies appears to bode promise, what awaits is a broad shallow pond of information – trials with modest samples sizes (median sample size of 26) conducted in an assortment of areas that range from purified food-related compounds, such as lycopene, to multicomponent behavioral interventions that include expansive shifts in dietary patterns accompanied by other lifestyle changes (i.e., increased exercise and stress reduction)[4,23, 24]. Given known selection bias against the publication of negative findings, it is unsurprising

that most of these studies have reported positive effects. Unfortunately, only about a quarter of these studies employed a randomized trial design. The 11 randomized diet-related clinical trials conducted to date are summarized in Table 1; the trials of single dietary constituents are featured first [25], followed by those that tested multiple components [26–30], and finally trials involving functional foods [31–34], and multi-behavior interventions involving diet, exercise and stress management therapies [35*] are presented last. While these 11 trials provide examples of the most rigorous dietary intervention trials conducted to date regarding prostate cancer, there still are significant limitations. In addition to the specific limitations documented within Table 1, the reader should note that sample sizes of these trials, while greater than the extant 28 studies that employed non-randomized designs, are still modest, the interventions are varied, and there is no consistency of findings. Thus, it is difficult, nor should clinicians generalize these findings for use within clinical practice. Indeed for much of this work, future trials are needed to truly discern benefit and perhaps more importantly, the absence of harm. Of course, the results of two major randomized, placebo-controlled trials loom on the horizon, the high profile Selenium and Vitamin E Cancer Prevention Trial (SELECT), a phase III randomized, placebo-controlled trial of selenium (200 µg/day from L-selenomethionine) and/or vitamin E (400 IU/day of all rac α -tocopheryl acetate) supplementation among 32,400 men [36*], and SWOG 9917 which is testing the effect of 200 µg/day of selenomethionine among 466 men with high-grade prostatic intraepithelial neoplasia [37*]. The results of SWOG 9917 and SELECT are anticipated in 2009 and 2013, respectively. Given the findings of a recent meta-analysis by Etminan *et al.* [38] which showed that selenium was associated with a protective effect on the prostate, there is reason to be cautiously optimistic. However, as previously mentioned, the recent findings related to vitamin E, as well as the past poor performance of dietary supplement trials in general, provides pause and a fair degree of skepticism.

If not supplements, then what?

In a review last year that focused on compelling current research and which made an attempt to distinguish findings which were ready to be translated into clinical practice from those which still required more investigation, weight management was named as a factor which appeared to yield the most promise [4]. The relationship between body weight status and prostate cancer continues to be an active area of research, and in the past 12 months roughly 20 more studies have appeared on this topic. Data which chronicle the course of obese and non-obese men receiving radiation therapy now join previous and even more data from surgical series which suggest that obesity is a risk factor for more aggressive and fatal prostatic carcinoma, though findings are mixed regarding its impact on immediate clinical outcomes, such as blood loss, operating room time, treatment recovery, etc. One of the most important papers to date on this subject was published in 2006 by MacInnes & English who reported a systematic review and meta-analysis on data from 31 cohort and 25 case-control studies (total of 68,753 cases and 2,779,563 controls) [39**]. Findings from this study indicate that for every 5 kg/m² unit increase in body mass index (BMI) the R.R.s were 1.05 (95% C.I.: 1.01–1.08) and 1.12 (95% C.I.: 1.01–1.23) for overall risk and advanced disease, respectively. The association between BMI and aggressive prostate cancer was further reinforced by two large cohort studies that were published earlier this year by Rodriguez *et al.* [40*] who analyzed data emanating from the Cancer Prevention Study II (5,252 incident cases in a cohort of 69,991 men), and Wright *et al.* [41*] who analyzed data from the NIH-AARP Diet and Health Study cohort (9986 incident cases in 287,760 men), though neither of these studies found evidence of the weaker association between higher BMI and overall disease risk. Both of these studies also contributed data regarding weight change and risk, with the study by Wright and colleagues finding that weight gain after age 18 was significantly associated with risk of fatal prostate cancer ($p=.009$), and the study by Rodriguez and colleagues suggesting that adult weight loss of at least 5 kg was protective for non-metastatic high grade prostate cancer (R.R.:0.58; 95% C.I. 0.43 - 0.79).

Thus, fairly solid evidence exists that obesity, especially that which develops over the course of adulthood, is a risk factor for aggressive prostate cancer, evidence that is mirrored in other cancers, as well (e.g., breast cancer). In view of these data, recent dietary guidelines established by both the American Cancer Society, as well as the World Cancer Research Foundation and American Institute for Cancer Research emphasize the importance of weight management [42**,43**], not only as a potential means to prevent and control cancer, but as a way to improve overall health. In seeming contrast, findings by Halabi et al. [44] reported earlier this year found that obesity was a significant predictor of overall survival and was protective against prostate cancer mortality in 1226 men enrolled in one of nine clinical trials that targeted advanced castration-recurrent disease. While such findings appear in direct opposition to those discussed earlier, end-stage disease may represent a unique example, or what Kalantar-Zadeh and colleagues refer to as the “risk factor paradox of wasting diseases [45].” Indeed, cancer-related cachexia has been documented for centuries, thus it is no surprise that once the machinery for active catabolism is turned on, it is those who are heaviest who are likely to survive the longest when the body starts eating itself [46]. Much like a meteor falling out of orbit, it is those with the largest mass that travel the greatest distances before the fire consumes them. Perhaps an interesting research question relates to when, in the course of disease, does catabolism begin? and does catabolism preempt the boney infiltration of tumor, or is it the progression of boney metastases which drives catabolism? Further study of the etiology of prostate cancer progression and the balance between anabolic and catabolic systems, their interplay with inflammatory pathways, and their ultimate impact on the skeleton, may provide valuable therapeutic insights [47,48*]. Freedland and Platz offer a thorough review of body weight and prostate cancer, and provide plausible explanations for the conundrum that exists regarding the associations between the two at various points during the course of disease, as well as the lifespan in general [49*].

In addition to weight management, recommendations also exist for a nutrient-dense diet that provides ample amounts of essential nutrients to nourish the body and prevent other diseases. Thus, while fruits, vegetables and whole grains may not play critical roles in prostate cancer prevention and control, Calorie per Calorie, these foods deliver more essential nutrients than almost any other food group, and also play an integral role in the prevention of cardiovascular disease [10**,42**]. Thus, a plant-based diet that is low in saturated and trans fats is recommended since statistics clearly show that men with prostate cancer are much more likely to succumb to a cardiovascular event than to die of their cancer [4,42**],

Conclusions—As with many cancer survivors, men with prostate cancer are often eager to make lifestyle changes [50.] While much more research is needed to determine nutritional factors that are important for prostate cancer prevention and control, the clinician who can seize the “teachable moment” of a cancer diagnosis to convey sound nutritional guidance can vastly improve the overall health of patients within their practices. Given the current state of the science regarding diet and prostate cancer, clinicians are advised to...

- Encourage patients to achieve a desirable weight through regular exercise and a healthful diet, knowing that there is good evidence that weight management is protective for prostate cancer and even better evidence that it is beneficial in preventing major forms of comorbidity such as cardiovascular disease and diabetes.
- Advocate the consumption of a nutrient dense diet that is rich in fruits, vegetables and whole grains, and low in saturated fat. While the role of dietary patterns is still unclear with regard to prostate cancer, these patterns are associated with lesser risk of hypertension and cardiovascular disease, and also increase the likelihood that nutrient needs are met [10**].

- Ask patients about their supplement-use. Point them to reliable resources and discourage supplements associated with known hazards, as well as doses that exceed known upper limits of safety [20]. Since currently there are no dietary supplements with proven value for prostate cancer, encourage patients to rely on food as a source of nutrients, rather than dietary supplements.
- Lead by example. Strive for a healthful weight, regular exercise and a nutrient-dense, low saturated fat diet.

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Table 1
Compilation of Nutrition-Related Randomized Controlled Trials Aimed at Prostate Cancer Prevention and Control

Research Team (year)	Sample Size & Description	Intervention	Design	Findings	Comments
Ansari et al. (2003)	54 pts w/metastatic CaP who had not been treated with other therapies	Lycopene (4 mg)	Arms: Orchiectomy alone (O) (27) or orchiectomy + lycopene supplement (OL) (27) Duration: 2 years	No differences between arms in PSA at 6 mths. At 24 mths, significant differences (p-values<.05) seen in O vs. OL arms in PSA [9.0 (7.5) vs. 3.0 (1.9) ng/dl, bone scan complete response 15% vs. 25%, & deaths 22% vs. 13%, respectively.	One of the few trials with bone scan & survival endpoints. Details of supplement not provided. While compelling, ability to generalize findings to US men is limited since most have had other forms of treatment.
Bunker et al. (2007)	80 "Afro-Caribbean" men w/ atypical biopsies or repeated negative biopsies w/elevated PSA	Lyc-O-Mato® tomato extract each capsule (15 mg Lycopene + 333 IU β-Carotene + 5.5 IU Vit. E (α-TE) + 1 mg phytofluene + 1 mg phytosterols (taken b.i.d.))	Arms: Multivitamin [MVI: 5000 IU Vit A activity + 30 IU Vit. E (α-TE) + 60 mg Vit. C + 20 µg selenium (SE)] (40) vs. MVI + Lyc-O-Mato® (40) Duration: 4 mths	PSA at baseline, 1 & 4 mths: MVI=5.31 (5.40), 4.63* (4.84), 5.39 (5.75) MVI+5.31 (5.37), 4.79 (4.24), 5.74 (4.99) Significant decreases in both arms at 1 mth, though MVI arm lower (P-values <.001). By 4mth both arms rebound	Trial illustrates importance of a control arm (since even greater decreases in PSA noted in this arm) & the need for longer follow-up (since initial effects were not sustained).
Kucuk et al. (2001)	26 CaP pts pre-prostatectomy	Lyc-O-Mato® as above	Arms: Lyc-O-Mato® (15) vs. standard of care (11) Duration: ~3 weeks	No significant between arm differences in PSA, but % of men w/multifocal HGPIN & prostate unconfined tumors significantly less w/Lyc-O-Mato (p<.05).	Trend toward more men w/ T ₁ CaP in intervention arm, not known if findings relate to intervention or to disease status.
Hoenjiet et al. (2005)	70 CaP pts w/rising PSAs post-XRT or prostatectomy or on active surveillance	750 mg Vit. C + 200 µg SE + 522 IU Vit. E + 200 mg Coenzyme Q10	Arms: Placebo (34) vs. Supplement (36) Duration: 21 weeks	No significant between arm differences in PSA,	No significant between arm differences in testosterone (T), sex hormone binding globulin (SHBG) or dihydro-T.
Kranse et al. (2005)	32 CaP pts w/rising PSAs post-XRT or prostatectomy or on active surveillance (AS)	75 IU Vit. E (α-TE) + 1500 mg phytosterols + 200 µg SE + Green Tea Extract + 60 mg genestein + 40 mg daidzein + 10 mg lutein + 10 mg lycopene + 10 mg palm carotenoids	Evenly assigned 6-week cross-over study (supplement vs. placebo) separated by 2-week wash-out	No differences between treatments for PSA doubling time. Free PSA increased during placebo & decreased with supplement (p=.02).	T & DHT levels significantly decreased on supplement (p-values <.02).
Schroder et al. (2005)	46 CaP pts w/rising PSAs post-XRT or prostatectomy	Lyc-O-Mato® + 62.5 mg soy isoflavones+160 mg Silymarin + 160 mg Vit C + 128 µg SE + 18 mg Zn + 4 mg ubiquinol + 5 mg Mn +2.7 mg CU+3 mcg Vit B +400 mcg folate+2.5 g Vit B ₂ +2.6 mg Vit B ₁₂ +500 mg N-acetyl L-cysteine	Evenly assigned 10-week cross-over design (supplement vs. placebo) separated by 4-week wash-out	The PSA slope (p = 0.03) & ² log PSA was significantly lower during the supplement phase.	Rationale for including each of constituents within this supplement is unclear

Research Team (year)	Sample Size & Description	Intervention	Design	Findings	Comments
Hamilton-Reeves et al. (2007)	58 men w/atypical biopsies (53) or w/low grade CaP on AS (5)	Soy Protein Isolate (SPI) 107 mg isoflavones Soy Protein Isolate w/ isoflavones extracted-out (SPI-) <6 mg isoflavones	SPI (20) vs. SPI- (20) vs. Milk Protein Control (18) Duration: 6 months	Baseline & 6 mth biopsies show AR expression (but not estrogen receptor- β) was significantly suppressed in SPI arm.	Significance of altering AR receptor is speculative. Sera (baseline, 3 & 6 mths) showed no between arm differences for T, free T, DHT, estradiol, estrone, SHBG, DHES & androstenedione. SPI- arm had significant decreases in androstenedione & estradiol from baseline.
Kumar et al. (2004)	59 CaP pts on AS	Soy Protein Beverage Supplement (60 mg genestein)	Soy Supplement (29) vs Isocaloric Placebo (30) Duration: 12 weeks	No between arm differences in mean change in PSA, though a higher % of soy arm had reductions in PSA ≥ 2 ng/dl	No between arm differences seen for SHBG, & free/total T & estradiol.
Dalais et al. (2004)	26 CaP pts pre-prostatectomy	50 g soy grits (SG) vs. 50 g soy grits + 20 g linseed (flaxseed) (SGL) both provided within bread	SG (8) vs. SGL (10) within bread & tested against wheat bread (WB) placebo (8) Duration: 3 weeks	Total PSA change scores significantly differed between SG & WB arms, -12.7 vs. +40%, respectively (p=.01). Change in free/total PSA was 27.4 vs. -15.6% in SG vs. SGL arms (p=.007)	Significant differences in change scores were seen for Free Androgen Index between SG & SGL arms, +16.4% vs. -15.5% (p=.04)
Bylund et al. (2003)	18 CaP pts on AS	Rye bread (RB) (295 g) vs. Wheat Bread (WB)(275 g) Control	RB (10) vs. WB (8) Duration: 3 weeks	Significant Ki-67 increases for both arms from pre-to-post biopsy. Apoptosis (TUNEL) significantly increased pre/post biopsy in RB arm (1.5 to 5.6), but not in WB (3.3 to 3.0). No differences over time or between arms for PSA.	No significant differences observed in change scores between arms with hormones associated with androgen, estrogen or insulin pathways.
Ornish et al. (2005)	90 CaP pts on AS	Low fat (<10% kcal)vegan diet + 1 serving soy/day + 3 g fish oil + 400 IU Vit. E + 200 μ g SE + 2000 mg Vit. C + stress reduction + exercise + group support	Intervention (41) vs. Usual Care Control (49) Duration: 12 months	Change in PSA was -4% in intervention arm & +6% in control arm (p=.016). Cell growth in LNCaP cells treated with pooled sera was -70% vs. -9% in intervention vs. control arms, respectively (p<.001)	Mean weight loss in experimental arm was 4.5 kg vs. 0 kg in controls. It is difficult to disentangle whether findings are due to intervention or to weight loss.

Table 2
Compilation of Nutrition-Related Randomized Controlled Trials Aimed at Prostate Cancer Prevention and Control

Research Team (year)	Sample Size & Characteristics	Intervention	Design	Findings	Comments
Ansari et al. (2003)	54 pts w/metastatic CaP who had not been treated with other therapies	Lycopene (4 mg)	Arms: Orchiectomy alone (O) (27) or orchiectomy + lycopene supplement (OL) (27) Duration: 2 years	At 6 mth, no differences between arms in PSA; at 24 mths mean values were O=9.0 (7.5) vs. OL=3.0 (1.9) ng/dl. Bone scan complete response in O vs. OL was 4 (15%) vs. 9 (25%), respectively. Deaths in O vs. OL arms were 12 (22%) vs. 7 (13%), respectively.	One of the few trials with bone scan & survival endpoints. Details of supplement not provided. While compelling, ability to generalize findings to US men is limited since # of men with metastatic disease is small and most have had other forms of treatment.
Bunker et al. (2007)	80 "Afro-Caribbean" men w/atypical biopsies or repeated negative biopsies w/ elevated PSA	Lyc-O-Mato® standardized tomato extract each capsule (15 mg Lycopene + 333 IU β-Carotene + 5.5 IU Vit. E (α-TE) + 1 mg phytofluene + 1 mg phytosterols (taken b.i.d.)	Arms: Multivitamin (MVI) (40) vs. MVI (40) + Lyc-O-Mato® (MVL) (40) MVI (5000 IU Vit A activity + 30 IU Vit. E (α-TE) + 60 mg Vit. C + 20 µg selenium) Duration: 4 mths	PSA at baseline, 1 & 4 mths: MVI=5.31 (5.40), 4.63* (4.84), 5.29 (5.75) MVL=5.31 (5.37), 4.79 (4.24), 5.74 (4.99) Significant decreases in both arms at 1 mth, though MVI arm lower (P-values <.001). By 4mth both arms rebound	Trial illustrates importance of a control arm (since even greater decreases in PSA noted in this arm) & the need for long term follow-up (since initial effects were not sustained).
Kucuk et al. (2001)	26 CaP pts pre-prostatectomy	Lyc-O-Mato® as above	Arms: Lyc-O-Mato® (15) vs. standard of care (11) Duration: ~3 weeks	No significant between arm differences in PSA, but % of men w/multifocal HGPIN & prostate unconfined tumors significantly greater in controls (p<.05).	Trend toward more men w/ T ₁ CaP in intervention arm, not known if findings relate to intervention or to cancer itself.
Hoenjiet et al. (2005)	70 CaP pts w/rising PSAs post-XRT/prostatectomy or on active surveillance	750 mg Vit. C + 200 µg selenium + 522 IU Vit. E + 200 mg Coenzyme Q10	Arms: Placebo (34) vs. Supplement (36) Duration: 21 weeks	No significant between arm differences in PSA.	No significant between arm differences in testosterone (T), sex hormone binding globulin (SHBG) or dihydro-T.
Kranse et al. (2005)	32 CaP pts w/rising PSAs post-XRT/prostatectomy or on active surveillance	75 IU Vit. E (α-TE) +1500 mg phytosterols + 200 µg selenium + Green Tea Extract + 60 mg genestein + 40 mg daidzein + 10 mg lutein + 10 mg lycopene + 10 mg palm carotenoids	Evenly assigned 6-week cross-over design (supplement vs. placebo) separated by 2-week wash-out	No differences between treatments for PSA doubling time. Free PSA doubling time significantly increased during placebo & decreased with supplement (p=.02).	T & DHT levels significantly decreased on supplement (p-values <.02).
Schroder et al. (2005)	46 CaP pts w/rising PSAs post-XRT/prostatectomy	Lyc-O-Mato® + 62.5 mg soy isoflavones+160 mg Silymarin + 160 mg Vit C + 128 µg selenium + 4 mg ubiquinol + 18 mg Zn + 2.7 mg CU + 5 mg Mn + 400 mcg folate + 2.6 mg Vit B ₁₂ + 3 mcg Vit B +	Evenly assigned 10-week cross-over design (supplement vs. placebo) separated by 4-week wash-out	The PSA slope (p = 0.03) & ² log PSA was significantly lower during the supplement phase.	Rationale for including each of constituents within this supplement is unclear

Research Team (year)	Sample Size & Characteristics	Intervention	Design	Findings	Comments
Hamilton-Reeves et al. (2007)	58 men w/atypical biopsies (53) or w/ low grade CaP on active surveillance (5)	2.5 g Vit B ₂ + 500 mg N- acetyl L-cysteine Soy Protein Isolate (SPI) 107 mg isoflavones Soy Protein Isolate w/ isoflavones extracted-out (SPI-) <6 mg isoflavones	SPI (20) vs. SPI- (20) vs. Milk Protein Control (18) Duration : 6 months	Baseline & 6 mth biopsies show AR expression (but not estrogen receptor-β) was significantly suppressed in SPI arm.	Significance of altering AR receptor is speculative. Sera (baseline, 3 & 6 mths) showed no between arm differences for estradiol, estrone, SHBG, androstenedione, DHES, DHT, T & free T. Significant decreases in androstenedione & estradiol in SPI- arm.
Kumar et al. (2004)	59 CaP pts on active surveillance	Soy Protein Beverage Supplement (60 mg genestein)	Soy Supplement (29) vs Isocaloric Placebo (30) Duration: 12 weeks	No between arm differences in mean change in PSA, though a higher % of soy arm had reductions in PSA ≥ 2 ng/dl	No between arm differences seen for SHBG, & free/total T & estradiol.
Dalais et al. (2004)	26 CaP pts pre-prostatectomy	50 g soy grits (SG) vs. 50 g soy grits + 20 g linseed (flaxseed) (SGL) both provided within bread	SG (8) vs. SGL (10) within bread & tested against wheat bread (WB) placebo (8) Duration: 3 weeks	Total PSA change scores significantly differed between SG & WB arms, -12.7 vs +40%, respectively (p=.01). Change in free/total PSA was 27.4 vs. -15.6% in SG vs. SGL arms (p=.007)	Significant differences in change scores were seen for Free Androgen Index between SG & SGL arms, +16.4% vs. -15.5% (p=.04)
Bylund et al. (2003)	18 CaP pts on active surveillance	Rye bread (RB) (295 g) vs. Wheat Bread (WB) (275 g) Control	RB (10) vs. WB (8) Duration : 3 weeks	Significant Ki-67 increases for both arms from pre-to-post biopsy. Apoptosis (TUNEL) significantly increased pre/post biopsy in RB arm (1.5 to 5.6), but not in WB (3.3 to 3.0). No differences over time or between arms for PSA.	No significant differences observed in change scores between arms with hormones associated with androgen, estrogen or insulin pathways.
Ornish et al. (2005)	90 CaP pts on active surveillance	Low fat (<10% of kcal), vegan diet + soy (1 serving) + fish oil (3g) + Vit. E (400 IU) + selenium (200 µg) + Vit. C (2000 mg) + stress reduction + exercise + group support	Intervention (41) vs. Usual Care Control (49) Duration: 12 months	Change in PSA was -4% in intervention arm & +6% in control arm (p=.016). Cell growth in LNCaP cells treated with pooled sera was -70% vs. -9% in intervention vs. control arms, respectively (p<.001)	Mean weight loss in experimental arm was 4.5 kg vs. 0 kg in controls. It is difficult to disentangle whether findings are due to intervention or to weight loss.