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Dietary Intervention in the Management of Prostate Cancer

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Abstract

Purpose of Review—This review synthesizes recent reports related to the dietary management of prostate cancer (CaP) into the existing body of science in an effort to best inform practice.

Recent Findings—Dietary factors are hypothesized to play a significant role in CaP, and have proven import for managing prevalent co-morbidities in this patient population (cardiovascular disease, diabetes and osteoporosis). Data regarding diet and CaP are accumulating and randomized controlled trials are 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 studies that have limitations in showing cause and effect. During the past year, the greatest and most consistent strides have been made in the area of energy balance, where data consistently show that overweight and obesity are associated with progressive disease and increased overall mortality.

Summary—To date, the strongest evidence regarding diet and CaP relates to energy balance. Urologists aspiring to best clinical practice should encourage their patients to achieve a healthful body weight through regular exercise and a healthful plant-based diet rich in fruits, vegetables and whole grains. Advocating functional foods or supplements explicitly for cancer control purposes is currently premature.

Keywords

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

Introduction

Lifestyle factors are associated with the etiology and progression of CaP. While diet is presumed to play a strong role in this disease, to date most data come from epidemiologic studies which are limited in establishing causality. During the past year, findings from additional observational research and preliminary data from pilot-feasibility studies have been published The purpose of this review is to acknowledge recent reports (published September 2005-December 2006) regarding weight management, dietary distribution, functional foods and dietary supplements in relation to CaP, and provide further commentary on significant factors that have implications for clinical practice.

Weight Management

The vast majority of papers appearing over the past year relate to body weight and its association with several outcomes in men diagnosed with CaP [1–15]. While little evidence exists that overweight and obesity increase risk for the development of CaP [4**,7], data are fast accumulating that show strong associations between obesity and progressive or aggressive

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disease and poorer overall outcomes; Table 1 provides summaries of original reports documenting disease-related endpoints. Indeed, most papers to date have documented poorer outcomes in men with higher body mass indexes. Body mass index (BMI=kg/m^2) is the most widely-used measure of adiposity, with standard BMI categories as follows: underweight <18.5; normal weight 18.5–24.9; overweight 25–29.9; obese (class I) 30–34.9; obese (class II) 35–39.9 and obese (class III) 40+ [16]. In the past year, one large multi-institutional study [2*], and four moderate-to-large single institution studies [5*,10,14*,15*] have confirmed previous findings that BMI is significantly and positively associated with biochemical and/or clinical failure. In these studies, BMI also was found to be associated with prognostic factors, i.e., higher Gleason sum, extraprostatic extension and clinical stage; however, even after adjustment for these factors, the associations with BMI remain significant. While Siddiqui *et al.* [13*] also found significant associations (p-values<.0.0001) between BMI, clinical stage and pathological Gleason sum, their analyses, which were adjusted for a variety of prognostic variables, suggest that BMI is not a significant independent risk factor for disease progression or survival (overall and disease-specific). Since the methodologic rigor of the study by Siddiqui *et al.* [13*] is exemplary (i.e., large sample with >10-year follow-up and careful statistical analysis), the discrepancies between this report and others may be explained by differences in their study sample, i.e., cases exclusive to the Mayo Clinic series and who had received treatment prior to the year 2000. As Freedland and colleagues [17] highlight in an earlier study, associations between BMI and biochemical recurrence appear stronger for patients diagnosed and treated more recently. While the mechanisms linking obesity to disease progression are not yet understood, a host of plausible explanations are offered and require further research (obesity reduces testosterone and creates a favorable environment for androgen-independent cell growth [4**], CaP is influenced by various lipokines and their associated genes [8,9,12], etc.).

Additionally, recent studies also have found that BMI is significantly associated with increased prostatic weight in younger men (<63 years), and thus may have implications for delayed diagnosis, and other urologic issues, such as benign prostatic hypertrophy [7]. Montgomery *et al.* found that obesity also is significantly associated with lower presurgical vitality (p=0.009), and delayed bowel recovery (p=0.01) and bother post-prostectomy (p=0.01) [10]. In a survey of 182 men post-prostatectomy, Mulholland and colleagues found that urinary incontinence was not associated with BMI, however it is unknown from their report if there were adequate numbers of obese and non-obese respondents to permit adequately-powered analysis [11].

In two separate reports emanating from one study, Basaria *et al.* [1] and Braga-Basaria *et al.* [3] also point to the problem of obesity in men receiving androgen deprivation therapy for advanced CaP. The initial report (N=53) [1] and a subsequent paper (N=58) [3] document findings that patients with metastatic disease, as compared to age-matched men with non-metastatic disease and healthy controls, had significantly higher BMIs and a higher incidence of metabolic syndrome and its associated biomarkers, e.g., leptin, insulin and glucose. Given that insulin-resistance contributes to diabetes and cardiovascular disease which are prevalent comorbidities among men with CaP [18,19], authors endorse the need for increased monitoring, especially among this subgroup of patients.

Thus, by-in-large most reports over the past year support the key role that body weight status plays, not only in progressive disease, but also in quality-of-life issues and co-morbidities prevalent among men with CaP. The importance of weight management also is underscored by the recent American Cancer Society (ACS) guidelines that have been explicitly established for cancer survivors [19].

Dietary Distribution/Dietary Patterns/Functional Foods

Compared to the large number of studies on body weight, comparatively fewer have explored dietary patterns and their association with CaP-related outcomes. During the past year, only one original report was published on this subject. A study by Chan and colleagues [20] on 1,202 loco-regional CaP cases within the Health Professionals Follow-up Study cohort explored associations between dietary intake post-diagnosis and progressive disease (evidenced by rising prostate specific antigen (PSA) levels or metastasis to the lymph nodes, bone or other organs). In analyses that were corrected for age at diagnosis, diet at pre-diagnosis and current energy intake and consumption of other food groups, they found significant protective associations for fish and tomato sauce, with Hazards Ratios (HR) of 0.52 (p=0.006) and 0.46 (p=0.04) for each daily serving increase, respectively. Additionally, "moderate," but non-significant protective associations were found for vegetable consumption. In contrast, milk was found to increase risk for progressive disease (HR=1.12; p=0.04 for each daily serving). Interestingly and in contrast to tomato sauce, raw tomato consumption also was significantly associated with risk; a HR of 1.27 (p=0.02) was observed for each daily serving of raw tomatoes. While the discrepancy regarding tomato consumption is difficult to resolve, the authors attribute it partly to differences in lycopene absorption, since lycopene (a carotenoid previously associated with a protective effect for CaP) is absorbed more readily from cooked, rather than raw tomatoes [20]. These results also provide support that omega-3 fatty acid intakes may be protective, as well as vegetable consumption overall. Therefore, like data regarding the importance of weight management, these data provide support for the ACS recommendations that suggest a plant-based diet [19]. The finding that milk consumption is significantly related to increased risk supports earlier findings that high calcium intakes, either through dairy products or supplements, may be associated with more aggressive disease [21]. This provides a conundrum for men treated with chemotherapy, hormonal therapy or surgical castration for advanced disease where treatment-induced bone loss is a concern and where current recommendations include weight-bearing exercise, and optimizing both vitamin D and calcium intakes [19,22,23]. Given conflicting findings for calcium [20,21,24], until more is known, men are encouraged to consume intakes consistent with the Dietary Reference Intake, i.e., 1000–1,200 mg/day [25], and to rely more on vitamin D to improve bone health (since accumulating data, including a recent prospective study on the Health Professionals Follow-Up cohort, suggest a benefit of higher intakes and circulating levels of vitamin D)[26].

In a highly publicized, yet modest-sized study, Ornish and colleagues [27,28] explored the feasibility and effects of an "intensive lifestyle intervention" that included several dietary elements mentioned above, as well as other components. In this pilot study, 93 patients on active surveillance for early stage CaP were randomized to usual care or to an arm assigned to a vegan diet supplemented with one daily serving of tofu and 58 g/day of a soy protein powdered beverage, 3 g/day of fish oil, 400 IU/day of vitamin E, 200 mcg/day of selenium, 2 g/day of vitamin C, regular aerobic exercise (30 minutes/day, 6 days/week), 1-hour/day of stress management, and 1-hour/week of support group participation. Men in the experimental arm were documented as having adherence rates of 95% thoughout the 12-month intervention. At follow-up, mean PSA levels decreased from 6.23 ng/ml to 5.98 ng/ml in the experimental arm and increased from 6.36 ng/ml to 6.74 ng/ml in the control arm (p=0.016). Furthermore, pooled sera from the experimental arm inhibited LNCaP cell growth by 70%, whereas sera from the control arm inhibited growth by only 9% (p<0.001). Compared to controls, men in the intervention arm also experienced significant reductions in blood lipids and improvements in quality-of-life [27,28]. While the results of this pilot study are intriguing, it remains unknown which elements, subsets of elements or whether the complex intervention in its entirety is needed to elicit favorable effects. The fact that men in the experimental arm experienced an average weight loss of 4.5 kg as compared to no net weight loss in the control arm, also may have confounded results. Further well-controlled and adequately-powered trials are needed

before such regimens can be generalized to the population at large or have implications on clinical practice.

Dietary Supplements

While there are a myriad of dietary supplements, this review will focus on Vitamin E, selenium and lycopene. These are areas where patient interest is high, recent reports exist and where randomized controlled trials (RCT) are underway.

The high profile Selenium and Vitamin E Cancer Prevention Trial (SELECT) has caused urologists and patients alike to view these supplements as beneficial, even though currently they remain unproven and data are still gathering [29]. Over the past year, observational data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which includes 29,361 men monitored for CaP indicate no relationship between the risk or progression of CaP and dietary or supplemental intakes of vitamins E and C or beta-carotene [30]. However, among current and recent smokers (tobacco-use in the past 10-years) reductions in the risk of advanced CaP(Gleason sum≥7, or stage III/IV) were observed with increasing doses of vitamin E. In this select subgroup of smokers, men taking ≥400 IU of vitamin E/day were observed to have a significant reduced risk (RR=0.29) of advanced CaP. Thus, vitamin E may have some potential applications for smokers in relation to CaP, however smoking cessation represents a more logical tact given its greater overall health benefits. This is especially important in view of the 2005 meta-analysis by Miller *et al.* [31]which showed significantly higher (p=0.035) all-cause mortality with ≥400 IU of vitamin E/day. Another concern regarding vitamin E or other high-dose antioxidants relates to their potential ability to reduce the efficacy of standard conventional treatments that rely on free radical production, e.g. radiation therapy. Results of a RCT of 540 head and neck patients receiving radiotherapy and randomized to 400 IU/day of vitamin E or placebo with 6.5 year median follow-up show a significantly higher all-cause mortality in those taking vitamin E (HR=1.38, 95% CI 1.03–1.85), and increased cause-specific mortality [32**]. While these findings are indirectly related to CaP, they provide a potentially useful paradigm.

Compared to vitamin E, little new data have been reported on selenium over the past year. A meta-analysis by Etminan *et al.* [33], continues to provide favorable suggestive findings and a feasibility study from the SELECT trial shows that l-selenomethionine supplement-use effectively increases selenium levels within the prostate [34]. Case-studies, however continue to accumulate that illustrate the dangers of hyperselenosis [35].

Clark et al. reported findings of the only trial that has studied the impact of lycopene supplementation on biochemically-recurrent CaP in patients after definitive localized treatment [36*]. This phase I/II dose escalating trial (15–120 mg/day) was conducted on six consecutive cohorts of 6 patients each who were studied for 1-year. The primary endpoint was PSA response defined as a 50% decline from baseline. None of the 35 patients completing the trial achieved a PSA response. Furthermore, a comparison of PSA doubling time during the study period and the year prior to study showed no differences (p=0.57); also, no differences were found in any other parameters of PSA kinetics. The form of lycopene used in this trial was identical to that used in a previous neoadjuvant study [37] and another small study of patients undergoing hormonal therapy for advanced disease [38,39].

Finally, given the potential role that supplement-use has in managing side effects of treatment, recent findings related to L-arginine supplement-use have particular relevance. L-arginine has been postulated as a treatment for erectile dysfunction, because of its effect on vascularization. Results of the Vascular Interaction With Age in Myocardial Infarction (VINTAGE MI) trial, a RCT of 153 patients post-MI randomized to 3 g L-arginine TID or placebo showed no differences in vascular endpoints [40]. The trial, however had to be stopped early due to higher

mortality in the supplement arm, thus necessitating a call-for-caution to patients who currently use this supplement.

Current Dietary Recommendations for Cancer Survivors

In 2006, the ACS released an updated guide for informed choices regarding diet and physical activity for cancer survivors [19]. These guidelines were established in response to the growing concern and potential opportunity to improve health in the rapidly expanding population of cancer survivors, now numbering >10.5 million and who represent 3–4% of the U.S. population (CaP survivors comprise the second largest group of survivors [~2 million])[41]. In developing these guidelines, the ACS assembled panels of experts who reviewed and synthesized current scientific evidence on diet and physical activity in relation to both cancer control and tertiary prevention. Some of the research presented in this review, as well as extant findings from years past, were considered in making these recommendations. Unsurprisingly, these current recommendations emphasize the importance of weight management and consumption of a plant-based diet that includes ample amounts of fruits, vegetables and whole grains, and minimal amounts of refined carbohydrates and saturated fat (Table 2). The section devoted to CaP also encourages men to adopt physically active lifestyles and to consume prudent diets that are moderate in calcium (1,000–1,200 mg/day) with at least 600 IU of vitamin D/day (not to exceed 10,000 IU/day). The report also acknowledges studies conducted on functional foods (e.g., soy and flaxseed), vitamins (e.g., vitamins D and E), micronutrients (e.g., selenium) and other food-related constituents (e.g., lycopene), but refrains from making recommendations in these areas given a lack of solid evidence and concern that most research relates to cancer prevention and may not apply to cancer control.

Translating Guidelines into Practice

Physicians are among the most powerful catalysts for promoting behavior change [42,43]. Thus, urologists and oncologists may be optimally-positioned to deliver sound dietary guidance to patients with CaP. Given time constraints, once physicians deliver initial health messages, more intensive health behavior counseling can be delegated to nurses, allied health personnel or to health behavior researchers who are actively testing novel interventions. An example of a home-based diet and exercise intervention that resulted in significant improvements in overall diet quality was recently reported by Demark-Wahnefried and colleagues [44]; more research is currently underway to explore the most effective means to improve patients' health behaviors.

Conclusions

More research is needed to determine dietary patterns and factors important for the management of CaP. However until more is known, patients should be encouraged to achieve a desirable weight through regular exercise and the consumption of a plant-based diet rich in fruits, vegetables and whole grains, moderate in calcium, ample in vitamin D, and low in saturated fat.

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Table 1

Original reports published between September 2005 and December 2006 that document associations between body weight status and disease-related outcomes in men diagnosed with prostate cancer

Research Team	Sample Size/Source	Sample Characteristics	Follow-up	Findings
Basaria, *et al.* [1] & Braga-Basaria, *et al*. [3*]	53 & 58 subjects from a single institution (Johns Hopkins)	Prostate cancer patients on androgen deprivation therapy, compared to non-metastatic cases and healthy controls (1st study N=18/17/18 & 2nd study 20/18/20)	At least12 months	These reports emanate from one study that shows that men on androgen deprivation therapy have significantly higher BMIs, prevalence of metabolic syndrome (p<.01); and biomarkers linked with metabolic syndrome, i.e., glucose (p=0.01), insulin (p=0.05), and leptin (p<0.01) than men who have non-metastatic disease or healthy controls.
Bassett, *et al.* [2*]	2,131 cases from multiple institutions (CaPSURE database)	Men receiving radical prostatectomy between 1989–2003	Median of 2 years	Significant associations found between BMI and recurrence (p=0.28). Men with BMIs of 35 + had a relative risk (RR) of recurrence of 1.69 (95% confidence interval [CI] 1.01–2.84)
Freedland, *et al.* [5*]	2,796 cases from a single institution (Johns Hopkins)	Men receiving radical prostatectomy between 1988–2004	Mean of 2.8 years	Significant associations found between BMI and high grade disease (p=0.03), positive surgical margins (p<0.001), extraprostatic extension (p<0.001), lymph node metastasis (p=0.01). Adjusted analyses show BMI is independently associated with biochemical recurrence (p<.001).
Freedland, *et al.* [6]	7,027 cases from a single institution (7 high volume surgeons at Johns Hopkins)	Men receiving radical prostatectomy between 1996–2004	NA	A significant and independent association (p=0.005) was found between BMI and capsular incision (surrogate for poor technical operation). Analaysis controlled for pre-op PSA, race, year of surgery, pathological Gleason sum, clinical stage, prostate weight, extraprostatic extension, seminal vesicle invasion.
Montgomery, *et al.* [10]	376 consecutive cases from a single institution (University of Michigan)	Men scheduled for radical prostatectomy between 2000-2003	Up to 3 years	In this survey study with an 80% response rate, BMI significantly associated with lower presurgical vitality

Research Team	Sample Size/Source	Sample Characteristics	Follow-up	Findings
				(p=0.0009), delayed bowel recovery (p=0.01) and bother (p=0.01), and PSA recurrence (p=0.05).
Mulholland, *et al.* [11]	182 cases	Men receiving radical prostatectomy	Up to 4.5 years	In this survey study with a 68% response rate, BMI was not significantly associated with urinary control, severity of stress incontinence, pad-use or quality of life related to urinary symptoms.
Siddiqui, *et al.* [13*]	5,313 cases from a single institution (Mayo Clinic)	Men receiving radical prostatectomy from 1990–1999	Median of 10.1 years	BMI significantly associated with clinical stage and pathological Gleason sum (p-values <0.0001), but not independently associated with recurrence or disease-specific or overall survival.
Strom, *et al.* [14*]	873 cases from a single institution (MD Anderson)	Men receiving external beam radiation for localized prostate cancer from 1988 – 2001	Median of 8 years	Obese men had an increased risk of both biochemical and clinical failure; the hazards ratios (HR) were 1.04 (95% CI 1.02–1.07) and 1.05 (95% CI 1.01–1.09), respectively.
Strom, *et al.* [15*]	526 cases from a single institution (MD Anderson)	Men receiving radical prostatectomy from 1992 – 2001	Mean of 4.5 years	A trend (p=0.07) was noted for biochemical failure among men with BMIs of 30+. Men who had gained over 1.5 kg/yr from age 25 to the time of diagnosis, had significantly higher rates biochemical failure (p=0.005).

Table 2

American Cancer Society Guidelines on Nutrition and Physical Activity

Maintain a healthy weight throughout life

- Balance caloric intake with physical activity
- Avoid excessive weight gain throughout the lifecycle
- Achieve & maintain a healthy weight if currently overweight or obese

Adopt a physically active lifestyle.

- Adults: engage in at least 30 minutes of moderate-to-vigorous physical activity, above usual activities, on five or more days of the week (45–60 minutes of intentional physical activity are preferable).
- Children & adolescents: engage in at least 60 minutes/day of moderate-to-vigorous physical activity at least 5 days per week.

Consume a healthy diet, with an emphasis on plant sources

- Choose foods & beverages in amounts that achieve & maintain a healthy weight.
- Eat five or more servings of a variety of vegetables & fruits each day.
- Choose whole grains in preference to processed (refined) grains.
- Limit consumption of processed & red meats.

If you drink alcoholic beverages, limit consumption (no more than one drink/day for women or two/day for men).