A Randomized Controlled Trial of a 6-Month Low-Carbohydrate Intervention on Disease Progression in Men with Recurrent Prostate Cancer: Carbohydrate and Prostate Study 2 (CAPS2)

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ABSTRACT

Purpose: Both weight loss and low-carbohydrate diets (LCD) without weight loss prolong survival in prostate cancer models. Few human trials have tested weight loss or LCD on prostate cancer.

Experimental Design: We conducted a multi-site randomized 6-month trial of LCD versus control on PSA doubling time (PSADT) in patients with prostate cancer with biochemical recurrence (BCR) after local treatment. Eligibility included body mass index (BMI) ≥ 24 kg/m^2 and PSADT 3 to 36 months. The LCD arm was instructed to eat ≤ 20 g/carbs/day; the control arm instructed to avoid dietary changes. Primary outcome was PSADT. Secondary outcomes included weight, lipids, glucose metabolism, and diet.

Results: Of 60 planned patients, the study stopped early after an interim analysis showed futility. Twenty-six LCD and 19 control patients completed the study. At 6 months, although both arms consumed similar protein and fats, the LCD arm reduced carbohydrates intake (-117 vs. 6 g, $P < 0.001$) and lost weight (-12.3 vs. -0.60 kg, $P < 0.001$). The LCD arm increased HDL and reduced triglycerides and HbA1c with no difference in total cholesterol or glucose. Mean PSADT was similar between LCD (22 months) and control (15 months, $P = 0.313$) arms. In a *post hoc* exploratory analysis accounting for prestudy PSADT, baseline PSA, primary treatment, and hemoconcentration, PSADT was significantly longer in LCD versus control (30 vs. 13 months, $P = 0.007$) arms. Adverse events were few, usually mild, and returned to baseline by 6 months.

Conclusions: Among BCR patients, LCD induced weight loss and metabolic benefits with acceptable safety without affecting PSADT, suggesting LCD does not adversely affect prostate cancer growth and is safe. Given exploratory findings of longer PSADT, larger studies testing LCD on disease progression are warranted.

Introduction

In U.S. men, prostate cancer is the most common noncutaneous cancer and second leading cause of cancer-related death (1). In 2019, it is estimated there will be 174,650 new cases and 31,620 deaths from prostate cancer (2). For men with nonmetastatic disease who require treatment, local therapy is not always curative. Although systemic therapies that improve overall survival in late-stage prostate cancer are being used earlier (chemotherapy and androgen-targeted therapy; refs. 3, 4), these therapies can have significant side effects. Newer alternatives with fewer side effects that compliment standard of care are urgently needed. In addition, because patients with prostate cancer often have an elevated risk for cardiovascular disease (CVD) already (5), alternative therapies that improve the patients' CVD risk profile are particularly preferred.

Approximately two thirds of U.S. men are overweight or obese (6). Our team and others found obese men are more likely to present with high-grade prostate cancer, progress to metastases, and die from prostate cancer (7–12). During a mean follow-up of 7.3 years in a retrospective cohort study of 1,337 men with localized prostate cancer who had received prostatectomy already, those who gained more than 2.2 kg had twice the recurrence risk (HR = 1.94; ref. 13). In addition, a meta-analysis of >18,000 men with prostate cancer found each 5 kg/m^2 body mass index (BMI) increase was linked with a 20% increased risk of prostate cancer death (7). In mice, weight loss by either restricting calories or placing mice in a colder environment results in slowed prostate cancer growth (14–16). Two randomized controlled trials (RCT) tested the effect of short-term weight loss on prostate cancer tissue biomarkers showing no benefits (17, 18). However, in both studies, the control arms lost weight, limiting comparison between treatment arms and weight loss was modest (<3% of body weight). Furthermore, our previous research found that higher BMI was associated with higher plasma volume and hemodilution of PSA and thus hemoconcentration from weight loss may result in artificial PSA rises, thereby obscuring prostate cancer benefits (19). Thus, despite clear human data linking obesity with prostate cancer progression and animal data linking weight loss with slowed prostate cancer growth, no human study, to date, tested significant weight loss (>5% body weight) versus no weight change on prostate cancer clinical behavior.

A meta-analysis of 48 weight loss RCTs in humans found a low-carbohydrate diet (LCD) resulted in the greatest weight loss (20). In

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Translational Relevance

Prostate cancer is the most common noncutaneous cancer and second leading cause of cancer-related death in men. Given local therapies are not always curative and systemic therapies have significant side effects, alternatives are needed. In prostate cancer models, both weight loss and low-carbohydrate diets (LCD) without weight loss prolong survival. We conducted a randomized trial of LCD versus control in men with a rising PSA after local therapy. The LCD was well-tolerated and induced significant weight loss. PSA doubling time (PSADT) was similar between arms. In *post hoc* analyses adjusting for baseline differences and the artificial PSA rise due to weight loss (hemoconcentration), a LCD significantly slowed PSADT. A LCD appears safe for patients with prostate cancer and does not adversely affect tumor growth. Larger studies testing whether a LCD slows disease progression are warranted given acceptable safety profiles and metabolic benefits of a LCD.

two prostate cancer xenografts comparing western and LCD, we found LCD without weight loss prolonged survival (21, 22) and slowed prostate cancer growth (23). These studies provided a rationale for testing the anti–prostate cancer effect of weight loss via an LCD in prostate cancer. The objective of this study was to test the effect of an LCD intervention versus usual care control on prostate cancer growth, for 6 months in men with biochemical recurrence (BCR) after definitive therapy for prostate cancer. Prostate cancer growth was measured by PSA doubling time (PSADT), a measure that is strongly correlated with death in men with recurrent prostate cancer (24).

Materials and Methods

Study design

After obtaining IRB approval at each site [Duke University Medical Center (DUMC, Durham, NC), Cedars-Sinai Medical Center (CSMC, Los Angeles, CA), Durham Veterans Affairs Medical Center (DVAMC, Durham, NC), and Maryland Chesapeake Urology Research Associates (MCURA, Catonsville, MD)], we conducted a multi-center phase II RCT of LCD versus a control arm. This study was conducted in accordance with the ethical guidelines of the U.S. Common Rule. Each patient signed a written consent. After confirming eligibility, patients completed a baseline visit and were randomized 1:1 to receive the LCD intervention or a no-dietary intervention control for 6 months. Randomization was conducted by permutated block design, stratified by center and BMI (<30 vs. ≥30 kg/m^2). Data collection occurred at baseline, 3 months, and 6 months postrandomization.

Intervention

The LCD arm was instructed by a dietitian to limit carbohydrate intake to ≤20 grams/day (25). Patients were provided a list of low-carbohydrate foods to choose from (e.g., greens, fats, lean meat, and seafood) and a list of moderate/high-carbohydrate foods to avoid (e.g., bread, pasta, grains, legumes, starchy vegetables). Grains and starchy vegetables are high in carbohydrates (e.g., 1 slice of bread contains about 12 g carbohydrate); thus, these food items were on the avoid list. Sample menus and recipes were also provided. No other limits were given. Patients were coached by the dietitian in person or by phone weekly during the first 3 months and biweekly for the last 3 months. During coaching, the study dietitian answered questions and provided necessary assistance to ensure dietary adherence among patients. Diet was assessed by 3-day food records (26) at each visit and analyzed by Food Processor software (ESHA, version 10.14). Patients in the LCD arm were asked to measure urinary ketone levels weekly using provided ketone strips (Ketostix, Bayer Healthcare). The ketone data were not formally collected but were shared with the study dietitian during coaching calls to assist with coaching. Control patients were asked to maintain usual dietary and exercise patterns.

Study patients

Key eligibility criteria included prior primary treatment for prostate cancer (radical prostatectomy or definitive local radiation including external beam radiation, brachytherapy, or both), PSA within the past two months of between 3 and 20 ng/mL if prior local radiation or between 0.4 and 20 ng/mL if prior radical prostatectomy, PSADT >3 and <36 months, BMI ≥24 kg/m^2, willingness to be randomized to either the LCD or the control arm, and phone access for calls. Key exclusion criteria included symptomatic metastatic disease, anticipation of needing secondary prostate cancer therapy within the next 6 months, current use of weight loss medications or enrollment in a diet/weight loss program, current therapy aimed at lowering testosterone levels (including GnRH agonist/antagonist, prior bilateral orchiectomy, oral anti-androgens, or 5-alpha reductase inhibitors; testosterone replacement was allowed but treatment should be stable during the entire study), already consuming an LCD, being vegetarian/vegan, unwilling to be randomized to either the LCD or control arm, weight loss >5% of body weight in the last 6 months based on self-report, or medical comorbidities that in the opinion of the investigator limits the patient's ability to complete the study.

Data collection and analysis

At each visit, weight (without shoes and in light clothing) and height were measured, fasting blood was collected, and adverse events (AE) were assessed. Fasting blood was analyzed for insulin, glucose, hemoglobin A1c (HbA1c), PSA, lipids, and high-sensitivity C-reactive protein (hsCRP). PSA, glucose, and lipids were measured by certified laboratories (LabCorp for DUMC, DVAMC, and MCURA; and Central Cedars-Sinai lab for CSMC). Insulin was measured in stored frozen serum in batch at the end of the study via an electrochemiluminescent immunoassay using an SI-2400 imager and assay kits from Meso Scale Discovery by Duke Immunoassay Laboratory. hsCRP was also measured by Duke Immunoassay Laboratory using high-sensitivity immunoturbidimetric assay by Beckman analyzer. AEs were rated as mild, moderate, or severe based on predetermined study definitions. Resting metabolic rate (RMR) was measured using a TrueMax 2400 Metabolic Cart (ParvoMedics) at baseline and 6 months only for patients enrolled at the DVAMC or DUMC.

Calculation of PSA outcomes

On-study PSADT was calculated as ln(2) divided by the slope of the linear regression line of ln(PSA) over time, using the baseline, 3, and 6-month on-study PSA values. Patients with negative or no PSA increase had PSADT converted to 120 months for ease of analysis, as in prior studies (24), to prevent undue influence on statistical inferences. We used all PSA values within 2 years prior to enrollment but after BCR (≥0.2 ng/mL for surgical patients and nadir plus ≥2 ng/mL for radiation patients) to calculate prestudy PSADT.

In *post hoc* exploratory analyses, the artificial rise in PSA due to weight loss, known as hemoconcentration, was also accounted for by using hemoconcentration-adjusted PSA values in calculating PSADT (19). The hemoconcentration-adjusted PSA, which denotes the total amount of PSA within circulation at the time of determination

of serum PSA concentration, was calculated as: serum PSA × total circulating plasma volume (19). The total circulating plasma volume was calculated as body surface area *X* 1.370 (27), where body surface area was calculated as (Weight$^{0.425}$ *X height*$^{0.72}$ *X* 0.007184; ref. 28).

Statistical analysis

The primary outcome was the difference in PSADT between the LCD and control arm over the 6-month study period. With 30 patients/arm, the *t* test had 80% power with an alpha of 0.05 to detect a difference of 0.73 standardized log-transformed PSADT units, corresponding to an increase in PSADT from 12.7 to 23.6 months. On the basis of data from our previous research (10, 24), this PSADT change would result in a predicted 60% reduction in the risk of prostate cancer–specific death and a 20% reduction in the risk for all-cause mortality for intervention versus control. Results are calculated and analyzed as the mean of log-transformed PSADT, but back transformed for presentation and interpretation.

An amendment to the study protocol was added to conduct a two-step interim analysis to test for efficacy and/or futility after 44 of the targeted 60 patients had completed the study. First, efficacy was assessed by comparing the mean PSADT between arms using a two-sided, two-sample *t* test at alpha level of 0.01. Next, given a nonsignificant efficacy test, treatment futility was assessed by calculating the conditional power of the *t* test given the interim data with conditional power <0.2 determining futility.

In *post hoc* exploratory analyses, we tested whether or not the number of patients with slower on-study versus prestudy PSADT differed between arms as well as whether the number of men who received prostate cancer treatment during the study differed by arm using Fisher exact test. After accounting for hemoconcentration (see above), we repeated the analyses assessing differences in continuous log-transformed PSADT and number of patients with PSADT slowed by arm. In further *post hoc* analysis, we used multivariable linear regression adjusted for treatment received (surgery vs. radiation), baseline PSA, and prestudy PSADT to assess the association between treatment arm and log-transformed PSADT (after accounting for hemoconcentration).

Intervention adherence was assessed by comparing self-reported changes in dietary intake from baseline to 6 months with the Wilcoxon rank sum test. Secondary outcomes included difference in RMR, body composition, and serum lab values between arms, which were examined as absolute or percent change from baseline to 6 months and tested using Wilcoxon rank sum test.

Statistical analyses were completed using SAS 9.4 (SAS Institute, Cary, NC). Two-sided $P < 0.05$ was considered statistically significant.

Results

A total of 78 patients signed a consent form of which 21 were either determined to be ineligible after further review of their records, withdrew, or lost to follow-up prior to randomization (**Fig. 1**). A total of 57 men were randomized to either the LCD arm ($n = 30$) or control ($n = 27$). The interim analysis concluded that the main outcome was not significant, and the conditional power was <0.2, and thus, the study was discontinued after a total of 45 patients completed the final study visit (26 LCD, 19 control). Their data were used for all analyses. Thus, the dropout rate was 13% ($n = 4$) in the LCD arm and 27% ($n = 8$) in the control arm. Reasons for drop out (**Fig. 1**) included starting treatment ($n = 3$ in LCD: 2 ADT prior to 3 months and 1 radiation prior to 6 months vs. $n = 6$ in control: 2 ADT prior to 3 months and 4 ADT prior to 6 months), lost to follow-up ($n = 1$ in control), and withdrawal ($n = 1$ in each group). During the study, although more men in the control arm went on to treatment (6/27) versus LCD arm (3/30), this difference was not statistically significant (Fisher exact, $P = 0.28$). Similarly, when only the 3- to 6-month time frame was evaluated, more men in the control arm went on to treatment (4/24) than the LCD arm (1/27), although this was not statistically significant (Fisher exact, $P = 0.17$).

Baseline characteristics

Baseline characteristics are presented in **Table 1**. Most patients (80%) received surgery as the prior primary prostate cancer treatment. Although differences were small, men in the LCD arm were more likely to have been treated with surgery, had lower PSA values and shorter PSADT values than controls. Both arms had similar baseline waist circumference, weight, BMI, RMR, and HbA1c. The LCD arm had higher total cholesterol, triglycerides, LDL cholesterol, but lower HDL cholesterol and glucose than the controls.

Primary outcome of PSADT

Per protocol, no difference was found in on-study log-transformed PSADT over the 6 months between arms using a *t* test (mean values in LCD vs. control: 22 vs. 15 months, $P = 0.313$; **Table 2**).

Post hoc exploratory analyses of PSADT

Relative to prestudy PSADT, LCD resulted in a greater proportion of patients whose PSADT was slowed (73%) versus controls (42%), although this did not reach statistical significance ($P = 0.064$; **Table 2**). When PSADT was adjusted for hemoconcentration, similar null results were observed for differences in continuous log-transformed PSADT by *t* test between LCD versus control (26 vs. 16 months, respectively, $P = 0.206$) and the proportion of patients with PSADT slowing remained nonsignificantly different than control patients ($P = 0.060$). Furthermore, after adjusting for key baseline covariates including baseline PSA, prestudy PSADT, treatment received (surgery vs. radiation), and accounting for hemoconcentration during the study, LCD significantly lowered log-transformed PSADT (30 vs. 13 months, $P = 0.007$). Similar findings were observed when race was also included in the models (data not shown). The other significant predictor of on-study PSADT was prestudy PSADT ($P = 0.002$).

Given the numerically higher dropout rate due to treatment in the control arm in the 3- to 6-month time frame, we were concerned that those with the most rapid PSADT were being excluded from the control arm creating an imbalance favoring the control arm. Therefore, we analyzed the PSADT data using only baseline and 3-month data. When this was done using the same strategies as described above, similar results were found (Supplementary Table S1). Without hemoconcentration adjustment, the PSADT in months was not significantly different between arms ($P = 0.391$) but the proportion of patients whose PSADT slowed was greater in the LCD arm (81%) compared with the control (45%) ($P = 0.015$). With hemoconcentration adjustment, the PSADT in months was not significantly different between the two arms ($P = 0.268$). However, the proportion of patients whose PSADT slowed was significantly greater in the LCD arm (81%) than in control (48%; $P = 0.018$). Similarly, the multivariable adjusted PSADT in months was also significantly longer in the LCD arm (31 months) compared with the control arm (15 months; $P = 0.047$) and remained significant after hemoconcentration adjustment ($P = 0.032$).

Secondary outcomes

Compared with men in the control arm, men in the LCD arm reduced their total calorie ($P = 0.004$) and carbohydrate intake

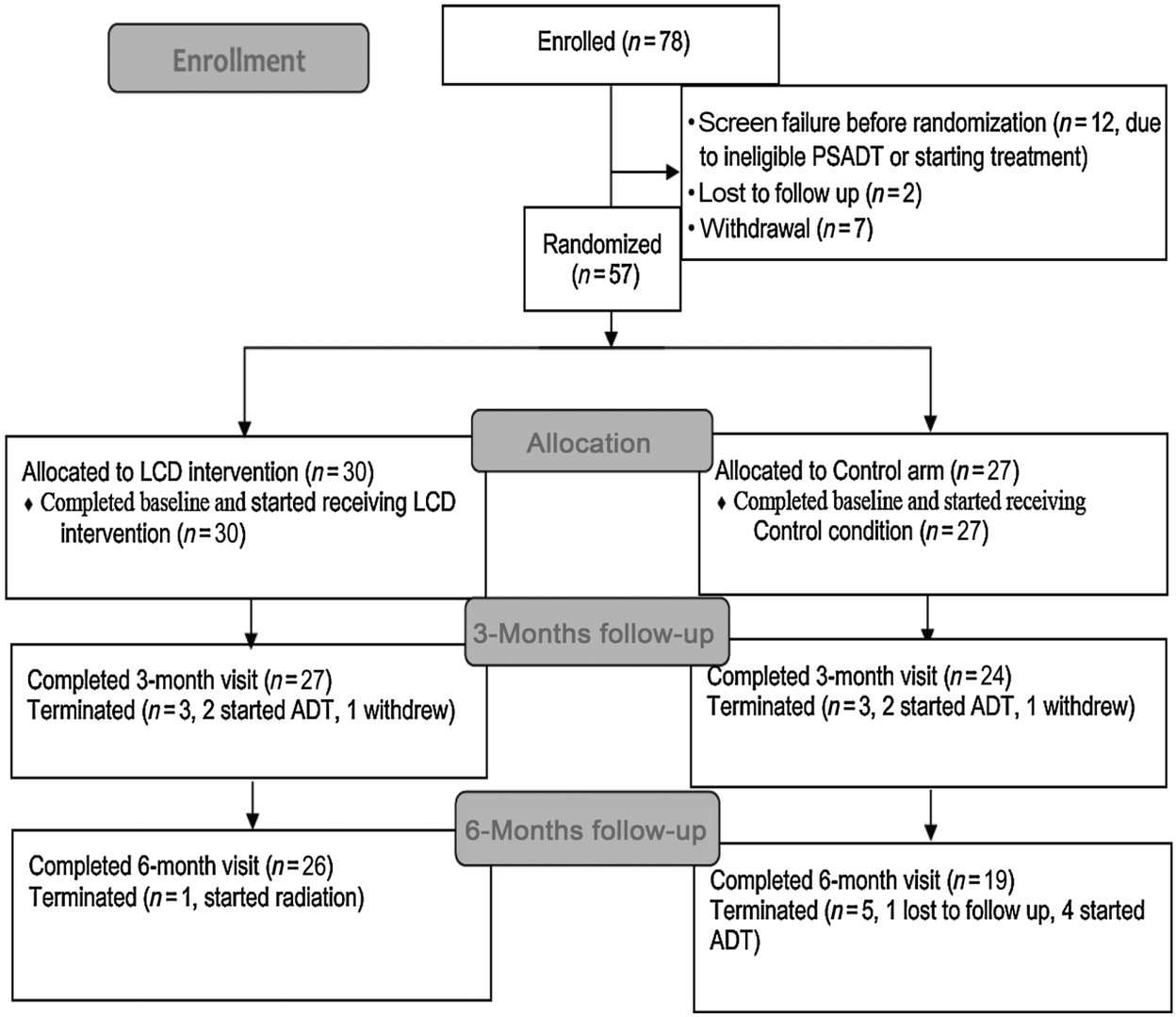

Figure 1.
Study CONSORT diagram.

(−117 vs. 6 g, $P < 0.001$) from baseline to 6 months (**Table 3**). The change in intake of macronutrients other than carbohydrates from baseline to 6 months was not significantly different between arms ($P \geq 0.121$).

As expected, at the end of the study (6 months), the LCD patients lost significantly more weight than controls (−12.3 vs. −0.60 kg, $P < 0.001$; **Table 4**). BMI and waist circumference were likewise reduced in LCD versus controls (BMI: −3.9 vs. −0.2 kg/m^2, waist circumference: −12.1 vs. −0.5 cm, both $P < 0.001$). Although RMR decreased more in LCD ($P = 0.029$), results were based on only 35 patients. Relative to baseline, the decline in triglycerides (−32 vs. −8 mg/dL, $P = 0.005$) and HbA1c (−0.4 vs. 0.0%, $P = 0.007$) were significantly greater and HDL was significantly increased (8.0 vs. −1.0 mg/dL, $P = 0.010$) in LCD versus controls. There were no significant differences in change in total cholesterol ($P = 0.290$), LDL ($P = 0.155$), fasting glucose ($P = 0.527$), and hsCRP ($P = 0.402$) between the two arms.

AEs

All AEs were mild except 1 moderate nausea at baseline and 3 months visit in the LCD arm and at baseline and 3 months in the control arm (Supplementary Table S2). At baseline, both LCD and control arms reported similar number of AEs (19 vs. 18, respectively). In the LCD, this increased to 27 at 3 months but returned to baseline ($n = 19$) at 6 months. In the control arm, there were 22 AEs at 3 months and 15 at 6 months. As expected, men in the LCD arm reported more constipation and fatigue at 3 months, but the frequency subsided to baseline by the 6-month visit. The control group had no major change in AEs during the study.

Discussion

With a scalable intervention approach, men in the LCD arm significantly reduced carbohydrate intake by about 75% (reduction of 117 g/day) from baseline to about 39 g/day while the control arm

Table 1. Baseline characteristics among patients who completed 6-month visit.

N (%) or median (IQR)	All men (*N* = 45)	LCD (*n* = 26)	Control (*n* = 19)
Age at visit, year	72 (66, 74)	71 (69, 74)	72 (65, 74)
Race, *n* (%)			
Asian	1 (2)	1 (4)	0 (0)
Black/African American	9 (20)	2 (8)	7 (37)
White/Caucasian	35 (78)	23 (88)	12 (63)
Site, *n* (%)			
DVAMC	11 (25)	4 (16)	7 (37)
WLA/VAMC	9 (20)	7 (28)	2 (11)
CURA	1 (2)	1 (4)	0 (0)
DUMC	24 (53)	14 (54)	10 (53)
Primary treatment, *n* (%)			
Surgery	36 (80)	23 (88)	13 (68)
Radiation	9 (20)	3 (12)	6 (32)
Waist girth (cm)	107.4 (103.8, 115.8)	106.7 (104.1, 113.8)	111.3 (100.9, 120.2)
Weight (kg)	196.8 (182.4, 216.0)	197.7 (177.9, 215.1)	195.6 (183.9, 235.5)
RMR, kcal/day[a]	1,670.0 (1,482.0, 1,834.0)	1,640.0 (1,393.0, 1,843.0)	1,701 (1,501, 1,747)
BMI, kg/m^2	29.3 (27.3, 32.5)	29.0 (27.9, 30.4)	29.7 (27.2, 32.9)
Cholesterol, mg/dL	162.0 (147.0, 189.0)	178.0 (147.0, 197.0)	157 (143.0, 175.0)
Triglycerides, mg/dL	106.0 (83.0, 139.0)	124.0 (83.0, 157.0)	94 (78.0, 139)
HDL cholesterol, mg/dL	47.0 (39.0, 55.0)	47.0 (39.0, 51.0)	50 (37.0, 60.0)
LDL cholesterol, mg/dL	90.5 (77.0, 114.0)	100 (79.0, 128.0)	89.0 (75.0, 105.0)
Glucose, mg/dL	100.0 (94.0, 110.0)	98.0 (93.0, 108.0)	107.0 (96.0, 115.0)
PSA, ng/mL	2.2 (0.9, 4.1)	1.5 (0.8, 3.3)	2.3 (0.9, 4.7)
PSADT, months	11 (8, 17)	11 (7, 16)	14 (10, 20)
hsCRP, mg/L	2.25 (1.12, 3.45)	2.16 (1.08, 3.38)	2.33 (1.16, 4.01)
HbA1c, %	5.8 (5.6, 6.3)	5.8 (5.5, 6.3)	5.8 (5.7, 6.2)

Abbreviation: IQR, interquartile range.
[a]Based on men with nonmissing values.

slightly increased by 6 g at the end of the 6-month intervention. Intake of other nutrients including protein, total fat, and fatty acids remained similar to baseline and similar between arms. Even though men in the LCD arm did not adhere to the target of intervention (20 g/day) perfectly, weight loss was significant and profound (12.3 kg) compared with controls wherein weight was relatively constant. Thus, our LCD intervention succeeded in reducing carbohydrate intake, reducing weight and BMI, and reducing waist circumference, which was associated with improvements in metabolic syndrome parameters and CVD risk factors (HbA1c, triglycerides, and HDL).

Table 2. Between arm comparison of PSADT with and without hemoconcentration adjustment among patients who completed all study visits.

	LCD (*n* = 26)	Control (*n* = 19)	*P*
Primary outcome			
PSADT in months (95% CI)[a]	22 (14–34)	15 (9–26)	0.313[b]
Post hoc analyses			
PSADT in months (95% CI)[a,c]	26 (18–37)	12 (8–18)	0.008[d]
PSADT slowed, *n* (%)	19 (73%)	8 (42%)	0.064[e]
PSADT^H in months (95% CI)[a]	26 (17–39)	16 (10–27)	0.206[b]
PSADT^H slowed, *n* (%)	20 (77%)	9 (47%)	0.060[e]
PSADT^H in months (95% CI)[a,c]	30 (21–43)	13 (8–20)	0.007[d]

Abbreviation: PSADT^H, PSA doubling time (adjusted for hemoconcentration).
[a]Mean and 95% CI are obtained from back-transforming results from a linear regression model with log PSADT as the outcome.
[b]*P* value obtained from *t* test
[c]Adjusted for baseline PSA, prestudy PSADT, and treatment received (surgery vs. radiation).
[d]*P* value obtained from multivariable linear regression model.
[e]*P* value obtained from Fisher exact test.

Despite these short-term metabolic changes and weight loss with the LCD intervention, our primary outcome of PSADT over a short-term period of 6 months was not significantly different between arms. Our findings suggest that weight loss via LCD may have a minimal short-term impact on tumor progression in patients with prostate cancer and a rising PSA disease state after local therapy. Only larger studies with longer term follow-up and monitoring for metastasis will be able to assess the impact of an LCD and weight loss on long-term PSA kinetics, metastasis free survival, and overall survival. In addition, our sample size was small and underpowered to exclude mild to moderate effect sizes on PSA kinetics between treatment arms, and thus, we cannot rule out a more modest impact on tumor progression.

In an exploratory, hypothesis-generating *post hoc* analysis that accounted for weight loss–induced hemoconcentration of PSA in each treatment arm over time and after adjusting for modest differences at baseline between treatment groups, we found that the LCD arm had significantly longer PSADT than the control arm at 6 months. A similar finding was also observed at 3 months. These findings need to be confirmed in future larger studies with longer term follow-up. However, if confirmed in future studies, this finding would be consistent with a previous animal study that examined LCD diets in prostate cancer (29) and showed that a 10% carbohydrate diet (45% fat, 45% protein) with weight loss reduced prostate cancer volume by 45%

Table 3. Summary CAPS2 dietary data by treatment arm among patients who completed study and have dietary data.

	LCD ($n = 26$)	Control ($n = 19$)	P^a
Total calorie (kcal)			
Baseline	1,643 (1,283, 1,901)	1,662 (1,298, 2,062)	—
Δ from baseline to 6 months	−92 (−507, 298)	157 (−88, 491)	0.004
Carbs (g)			
Baseline	156 (101, 190)	182 (119, 238)	—
Δ from baseline to 6 months	−117 (−142, −70)	6 (−47, 49)	<0.001
Protein (g)			
Baseline	79 (67, 100)	85 (58, 99)	—
Δ from baseline to 6 months	31 (1, 58)	11 (−11, 27)	0.195
Total fat (g)			
Baseline	71 (43, 88)	72 (55, 94)	—
Δ from baseline to 6 months	20 (−2, 38)	7 (−16, 21)	0.121
Saturated fat (g)			
Baseline	17 (10, 25)	21 (14, 29)	—
Δ from baseline to 6 months	9 (2, 19)	1 (−8, 13)	0.167
Polyunsaturated fat (g)			
Baseline	13 (9, 20)	13 (11, 20)	—
Δ from baseline to 6 months	1 (−5, 7)	−1 (−3, 7)	0.877
Monounsaturated fat (g)			
Baseline	25 (14, 29)	19 (16, 27)	—
Δ from baseline to 6 months	8 (5, 15)	4 (1, 20)	0.464

[a]Wilcoxon rank sum test.

($P < 0.001$). Even though our previous animal models showed that the magnitude of prostate cancer tumor volume growth was slowed similarly despite carbohydrate intake restrictions of 0%, 10%, or 20% kcal without weight loss (30), it is unclear if similar effects are true in humans. In our current study, we used PSADT during the study as the sole measure of tumor growth. However, PSA values (and hence PSADT) can be influenced by weight change and change in blood volume (19). In addition, it is known that the natural history of PSA changes over time can include PSA reductions or slowing, and thus larger and longer randomized trials are required in this setting (31). In addition, whether greater compliance to the LCD intervention would have led to slowed PSADT remains to be tested. It would also be important for future studies to examine whether patients continue to adhere to an LCD even once they are "off study" and how this may impact any potential benefits of an LCD.

When future studies are conducted to examine the effect of LCD on PC growth, we propose that two key potential mechanisms be explored: (i) reduced insulin-like growth factor (IGF) axis signaling and (ii) reduced tumor inflammation signaling. In addition, in a previous animal model (32, 33), we found that 93 gene expression pathways were enriched or depressed in the LCD arm versus Western diet arm, suggesting many other pathways may mediate the effects of LCD. One proposed, but poorly studied mechanism to explain all of these effects, is an altered epigenome (34). Indeed, previous research

Table 4. Absolute changes in weight, BMI and RMR, glucose metabolism markers, lipids, and PSA from baseline to 6 months among those who completed the study.

	Median (IQR)		
Absolute change in:	LCD ($n = 26$)	Control ($n = 19$)	P^a
Weight, kg	−12.3 (−15.1, −8.7)	−0.6 (−1.9, 1.0)	<0.001
BMI, kg/m^2	−3.9 (−5.2, −2.7)	−0.2 (−0.6, 0.3)	<0.001
Waist girth, cm	−12.1 (−14.7, −7.0)	−0.5 (−3.2, 0.7)	<0.001
RMR, calories/day[b]	−204 (−306.0, −71)	−26.0 (−182, 91)	0.029
PSA, ng/mL	0.5 (0.0, 2.0)	0.6 (0.3, 1.9)	0.231
Cholesterol, mg/dL	12.0 (−10.0, 24.0)	−3 (−14.0, 18.0)	0.290
Triglycerides, mg/dL	−32.0 (−68.0, −18.0)	−8.0 (−28.0, 7.0)	0.005
HDL cholesterol, mg/dL	8.0 (2.0, 18.0)	−1 (−4.0, 6.0)	0.010
LDL cholesterol, mg/dL	8.0 (−11.0, 25.0)	−2.0 (−13.0, 9.0)	0.155
Glucose, mg/dL	−5.0 (−12.0, 4.0)	1.0 (−10.0, 7.0)	0.527
hsCRP, mg/L	0.0 (−0.6, 0.7)	−0.1 (−0.7, 0.2)	0.402
HbA1c, %	−0.4 (−0.6, −0.1)	0.0 (−0.2, 0.1)	0.007

Abbreviation: IQR, interquartile range.
[a]Wilcoxon rank sum test.
[b]Based on men with nonmissing values.

has shown that a ketogenic diet (a form of LCD) alters the brain epigenome, with changes maintained even after stopping the diet for 8 weeks (35). Thus, exploring the potential underlying mechanisms may shed light on the responsiveness or the lack thereof among patients with prostate cancer to weight loss via an LCD intervention.

The typical Western diet contains 40% to 60% kcals as carbohydrates. LCDs, defined as ≤20% carbohydrate kcals (36), are used for epilepsy (37) and for weight loss (38–40). There is growing interest in ketogenic diets for diabetes and weight loss (41). In regards to heart disease (a concern often mentioned for LCD), carbohydrate restriction lowers triglycerides and cholesterol and raises HDL, which is sustained up to 2 years (38, 42). Furthermore, a study of >135,000 people in 18 countries from 5 continents followed for 7.4 years found higher carbohydrate intake was linked with higher death risk ($P < 0.001$; ref. 43). Because LCDs may result in varying amounts of carbohydrate, protein, and fat intakes, future research should include clearer definitions in at least macronutrient intakes. In the current study, we recognized the concern of high saturated fat intake that often accompanies LCDs (>20% kcal); thus, we emphasized a healthy version of fat intake in the intervention. To accomplish this, patients were asked to limit foods with high saturated fat such as fatty meats and butter. Instead, they were encouraged to consume lean meats cooked with healthy fats including olive oils. This effort was reflected in the only slight and nonsignificant increase in saturated fat in the LCD arm relative to controls and was lower than seen in other LCD studies (44).

Another potential concern regarding the LCD is in its inconsistent impact on LDL cholesterol. A meta-analysis of 11 RCTs concluded that the beneficial changes of LCDs in weight loss should be weighed against the possible detrimental effects of increases in LDL (45). This is important in that some data suggest higher cholesterol may be linked with more aggressive prostate cancer (46), although controversy exists on this topic (47). Nonetheless, in the current study, we found no significant change in either total or LDL cholesterol between arms, which may reflect either small sample sizes or our focus on "healthier" meats for men on the LCD. In a cross-sectional analysis, a LCD was not associated with increased risk for metabolic syndrome but may moderately increase HDL cholesterol (48). In addition, consistent with our findings, two meta-analyses showed that LCDs significantly improved HbA1c, reduced triglycerides, and increased HDL, all of which are important diabetes and CVD risk factors (49, 50). Thus, LCDs are effective for weight loss and may improve multiple risk factors for CVD. This is an important finding because CVD and other chronic diseases including diabetes are major causes of death among patients with prostate cancer (51).

In the current study, common AEs observed in previous LCD interventions were also reported including constipation and fatigue, which were slightly higher in the LCD arm. Importantly, these resolved by 6 months and no new safety concerns were observed.

There are limitations in our study. First, the small sample size may have limited the detection of the true association between weight loss via LCD and change in PSADT. Indeed, in unadjusted analysis, there was a 17-month longer PSADT in the LCD arm, although this was not significant. If a large study confirmed this degree of longer PSADT, it would have strong clinical relevance. Second, we cannot separate effects of weight loss from carbohydrate restriction. As the combined intervention of weight loss via LCD may confer a greater effect than either alone, future research is needed to test the separate effects if the combined intervention effect on prostate cancer is proven to be significant in future studies. Third, the study intervention was short term and only a surrogate marker of tumor growth (PSADT) was used. Future studies with longer term follow-up and use of harder endpoints is needed. If the benefit of LCD on prostate cancer is confirmed in future studies, subsequent research will be needed to examine whether any dose–effect relationship exists and to develop effective strategies for long-term sustainability. Also, our intervention focused on diet changes only. Whether a whole lifestyle intervention (diet + exercise) would have greater effects requires further study.

Our study also has strengths. This is the first human study to examine and demonstrate that an LCD is safe in men with BCR, is feasible and effective for weight loss, and does not adversely affect prostate cancer growth. Whether an LCD has benefits to slow cancer progression or other long-term outcomes such as prostate-specific or overall mortality requires larger studies. To date, very few published studies have prospectively examined dietary interventions such as the LCD for cancer treatment. Our team examined LCD among patients with prostate cancer initiating androgen deprivation therapy (ADT) and found the LCD was effective for weight loss and may potentially reduce the risk for common side effects of ADT (25). Another case report suggested that LCD may have a potential benefit in two pediatric patients with malignant astrocytoma (52).

In conclusion, an LCD intervention among men with BCR results in significant weight loss, improvements in HDL, and reductions in triglycerides and HbA1c with no impact on PSA kinetics. In a *post hoc* exploratory analysis, there was a suggestion that PSADT may be slowed after accounting for weight loss–induced hemoconcentration and baseline confounders. Future larger studies are thus needed to test the potential benefits of a LCD with more reliable surrogates of tumor growth and cancer-specific mortality, such as metastasis-free survival (53). However, for men who desire the metabolic and weight loss benefits of LCD, our data support its use for men with BCR given an acceptable toxicity profile and no adverse effect on tumor growth.

Disclosure of Potential Conflicts of Interest

A.J. Armstrong reports receiving other commercial research support from Astellas, Janssen, and Pfizer and speakers bureau honoraria from Dendreon and Bayer. H. Sandler is an employee/paid consultant for Janssen and holds ownership interest (including patents) in Radiogel. No potential conflicts of interest were disclosed by the other authors.

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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
2. American Cancer Society. Key statistics for prostate cancer. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html#references. 2019 [updated 2019 Jan 8].
3. Sweeney CJ, Chen Y-H, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.
4. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.
5. Leong DP, Fradet V, Shayegan B, et al. Cardiovascular risk in men with prostate cancer: insights from the RADICAL PC Study. J Urol 2020 Jan 3 [Epub ahead of print].
6. Centers for Disease Control and Prevention. Disability and risk factors: obesity and overweight. Atlanta, GA: Centers for Disease Control and Prevention; 2017. Available from: https://www.cdc.gov/nchs/fastats/obesity-overweight.htm.
7. Cao Y, Ma J. Body mass index, prostate cancer-specific mortality, and biochemical recurrence: a systematic review and meta-analysis. Cancer Prev Res 2011;4:486–501.
8. Rodriguez C, Freedland SJ, Deka A, Jacobs EJ, McCullough ML, Patel AV, et al. Body mass index, weight change, and risk of prostate cancer in the Cancer Prevention Study II Nutrition Cohort. Cancer Epidemiol Biomarkers Prev 2007;16:63–9.
9. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol 2013;63:800–9.
10. Freedland SJ, Aronson WJ, Kane CJ, Presti JC, Amling CL, Elashoff D, et al. Impact of obesity on biochemical control after radical prostatectomy for clinically localized prostate cancer: a report by the Shared Equal Access Regional Cancer Hospital database study group. J Clin Oncol 2004;22:446–53.
11. Keto CJ, Aronson WJ, Terris MK, Presti JC, Kane CJ, Amling CL, et al. Obesity is associated with castration-resistant disease and metastasis in men treated with androgen deprivation therapy after radical prostatectomy: results from the SEARCH database. BJU Int 2012;110:492–8.
12. Ma J, Li H, Giovannucci E, Mucci L, Qiu W, Nguyen PL, et al. Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. Lancet Oncol 2008;9:1039–47.
13. Joshu CE, Mondul AM, Menke A, Meinhold C, Han M, Humphreys EB, et al. Weight gain is associated with an increased risk of prostate cancer recurrence after prostatectomy in the PSA era. Cancer Prev Res 2011;4:544–51.
14. Mukherjee P, Sotnikov AV, Mangian HJ, Zhou J-R, Visek WJ, Clinton SK. Energy intake and prostate tumor growth, angiogenesis, and vascular endothelial growth factor expression. J Natl Cancer Inst 1999;91:512–23.
15. Hursting SD, Lavigne JA, Berrigan D, Perkins SN, Barrett JC. Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans. Annu Rev Med 2003;54:131–52.
16. Huffman DM, Johnson MS, Watts A, Elgavish A, Eltoum IA, Nagy TR. Cancer progression in the transgenic adenocarcinoma of mouse prostate mouse is related to energy balance, body mass, and body composition, but not food intake. Cancer Res 2007;67:417–24.
17. Demark-Wahnefried W, Rais-Bahrami S, Desmond RA, Gordetsky JB, Hunter GR, Yang ES, et al. Presurgical weight loss affects tumour traits and circulating biomarkers in men with prostate cancer. Br J Cancer 2017;117:1303–13.
18. Henning SM, Galet C, Gollapudi K, Byrd JB, Liang P, Li Z, et al. Phase II prospective randomized trial of weight loss prior to radical prostatectomy. Prostate Cancer Prostatic Dis 2018;21:212–20.
19. Banez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, Rodriguez C, et al. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. JAMA 2007;298:2275–80.
20. Johnston BC, Kanters S, Bandayrel K, Wu P, Naji F, Siemieniuk RA, et al. Comparison of weight loss among named diet programs in overweight and obese adults: a meta-analysis. JAMA 2014;312:923–33.
21. Mavropoulos JC, Buschemeyer WC, Tewari AK, Rokhfeld D, Pollak M, Zhao Y, et al. The effects of varying dietary carbohydrate and fat content on survival in a murine LNCaP prostate cancer xenograft model. Cancer Prev Res 2009;2:557–65.
22. Freedland SJ, Mavropoulos J, Wang A, Darshan M, Demark-Wahnefried W, Aronson WJ, et al. Carbohydrate restriction, prostate cancer growth, and the insulin-like growth factor axis. Prostate 2008;68:11–9.
23. Allott EH, Macias E, Sanders S, Knudsen BS, Thomas GV, Hursting SD, et al. Impact of carbohydrate restriction in the context of obesity on prostate tumor growth in the Hi-Myc transgenic mouse model. Prostate Cancer Prostatic Dis 2017;20:165–71.
24. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294:433–9.
25. Freedland SJ, Howard L, Allen J, Smith J, Stout J, Aronson W, et al. A lifestyle intervention of weight loss via a low-carbohydrate diet plus walking to reduce metabolic disturbances caused by androgen deprivation therapy among prostate cancer patients: carbohydrate and prostate study 1 (CAPS1) randomized controlled trial. Prostate Cancer Prostatic Dis 2019;22:428–37.
26. Thompson FE, Kirkpatrick SI, Subar AF, Reedy J, Schap TE, Wilson MM, et al. The National Cancer Institute's Dietary Assessment Primer: A Resource for Diet Research. J Acad Nutr Diet 2015;115:1986–95.
27. Boer P. Estimated lean body mass as an index for normalization of body fluid volumes in humans. Am J Physiol 1984;247:F632–6.
28. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 1989;5:303–11.
29. Venkateswaran V, Haddad AQ, Fleshner NE, Fan R, Sugar LM, Nam R, et al. Association of diet-induced hyperinsulinemia with accelerated growth of prostate cancer (LNCaP) xenografts. J Natl Cancer Inst 2007;99:1793–800.
30. Masko EM, Thomas JA, Antonelli JA, Lloyd JC, Phillips TE, Poulton SH, et al. Low-carbohydrate diets and prostate cancer: how low is "low enough"? Cancer Prev Res 2010;3:1124–31.
31. Smith MR, Manola J, Kaufman DS, George D, Oh WK, Mueller E, et al. Rosiglitazone versus placebo for men with prostate carcinoma and a rising serum prostate-specific antigen level after radical prostatectomy and/or radiation therapy. Cancer 2004;101:1569–74.
32. Bedolla R, Prihoda TJ, Kreisberg JI, Malik SN, Krishnegowda NK, Troyer DA, et al. Determining risk of biochemical recurrence in prostate cancer by immunohistochemical detection of PTEN expression and Akt activation. Clin Cancer Res 2007;13:3860–7.
33. Kreisberg JI, Malik SN, Prihoda TJ, Bedolla RG, Troyer DA, Kreisberg S, et al. Phosphorylation of Akt (Ser473) is an excellent predictor of poor clinical outcome in prostate cancer. Cancer Res 2004;64:5232–6.
34. Labbe DP, Zadra G, Ebot EM, Mucci LA, Kantoff PW, Loda M, et al. Role of diet in prostate cancer: the epigenetic link. Oncogene 2015;34:4683–91.
35. Lusardi TA, Akula KK, Coffman SQ, Ruskin DN, Masino SA, Boison D. Ketogenic diet prevents epileptogenesis and disease progression in adult mice and rats. Neuropharmacology 2015;99:500–9.
36. Westman EC, Mavropoulos J, Yancy WS, Volek JS. A review of low-carbohydrate ketogenic diets. Curr Atheroscler Rep 2003;5:476–83.
37. Kossoff EH. More fat and fewer seizures: dietary therapies for epilepsy. Lancet Neurol 2004;3:415–20.
38. Yancy WS Jr, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet versus a low-fat diet to treat obesity and hyperlipidemia: a randomized, controlled trial. Ann Intern Med 2004;140:769–77.
39. Stern L, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140:778–85.
40. Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–90.
41. Abbasi J. Interest in the ketogenic diet grows for weight loss and type 2 diabetes. JAMA 2018;319:215–7.
42. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. N Engl J Med 2008;359:229–41.
43. Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet 2017;390:2050–62.
44. Zajac A, Poprzecki S, Maszczyk A, Czuba M, Michalczyk M, Zydek G. The effects of a ketogenic diet on exercise metabolism and physical performance in off-road cyclists. Nutrients 2014;6:2493–508.
45. Mansoor N, Vinknes KJ, Veierod MB, Retterstol K. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: a meta-analysis of randomised controlled trials. Br J Nutr 2016;115:466–79.

46. Jamnagerwalla J, Howard LE, Allott EH, Vidal AC, Moreira DM, Castro-Santamaria R, et al. Serum cholesterol and risk of high-grade prostate cancer: results from the REDUCE study. Prostate Cancer Prostatic Dis 2018;21:252–9.
47. YuPeng L, YuXue Z, PengFei L, Cheng C, YaShuang Z, DaPeng L, et al. Cholesterol levels in blood and the risk of prostate cancer: a meta-analysis of 14 prospective studies. Cancer Epidemiol Biomarkers Prev 2015;24:1086–93.
48. Ha K, Joung H, Song Y. Low-carbohydrate diet and the risk of metabolic syndrome in Korean adults. Nutr Metab Cardiovasc Dis 2018;28:1122–32.
49. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: A systematic review and meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2017;131:124–31.
50. Huntriss R, Campbell M, Bedwell C. The interpretation and effect of a low-carbohydrate diet in the management of type 2 diabetes: a systematic review and meta-analysis of randomised controlled trials. Eur J Clin Nutr 2018;72:311–25.
51. Epstein MM, Edgren G, Rider JR, Mucci LA, Adami HO. Temporal trends in cause of death among Swedish and US men with prostate cancer. J Natl Cancer Inst 2012;104:1335–42.
52. Nebeling LC, Miraldi F, Shurin SB, Lerner E. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. J Am Coll Nutr 1995;14:202–8.
53. Xie W, Regan MM, Buyse M, Halabi S, Kantoff PW, Sartor O, et al. Metastasis-free survival is a strong surrogate of overall survival in localized prostate cancer. J Clin Oncol 2017;35:3097–104.