

# Including Extra Virgin Olive Oil May More Improve Glycemic Control despite Similar Weight Loss Compared to the Diet Recommended by the Prostate Cancer Foundation: A Randomized, Pilot Study

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## Abstract

Recommendations for prostate cancer treatment include weight loss, but the most efficacious diet has not been determined. Men on active surveillance or with untreated biochemical relapse consumed both the diet recommended by the Prostate Cancer Foundation (PCF) and a plant-based that included three tablespoons of extra virgin olive oil per day for 8 weeks of weight loss and improvement in some laboratory biomarkers with random assignment to the diet order. They then selected one of the diets for six months of follow-up. Thirty men started the protocol and 18 completed the 44 week study. Mean age: 66.6  $\pm$  5.9 years; baseline body mass index: 30.9  $\pm$  2.7 kg/m<sup>2</sup>. Weight loss was comparable between the diets after 8 weeks (PCF:  $2.5\% \pm 3.1\%$  v olive oil: 2.8%  $\pm$  3.7%; p = 0.86), but the diet that included olive oil resulted in lower insulin (PCF:  $13.7 \pm 7.0 \text{ mU/L v}$  olive oil:  $11.5 \pm 4.4 \text{ mU/L}$ ; p = 0.02), glucose (PCF:  $104.9 \pm 9.9 \text{ mg/dl v } 99.1 \pm 9.6 \text{ mg/dl}; p = 0.01$ ), and HOMA-IR (PCF:  $3.6 \pm 2.1$  v olive oil:  $2.9 \pm 1.2$ ; p = 0.02). Thirteen of the 18 men choose the olive oil diet for six months of follow-up and weight loss and lab improvements were maintained. This pilot study indicates that both the PCF diet and the plant-based diet that included extra virgin olive oil can produce similar weight loss short-term. However, a plant-based diet that includes extra virgin olive may be more acceptable for long-term use, and produce better glycemic control.

## **Keywords**

Prostate Cancer, Extra Virgin Olive Oil, Weight Management

#### **1. Introduction**

Dietary treatment for prostate cancer includes weight loss, as cancer recurrence [1], risk of metastasis, and mortality [2] [3] are all positively related to body weight. Studies comparing diets with a range of nutrient composition show that weight loss does not differ by diet composition, but is related to adherence [4]. The diet prescribed should lead to healthy weight loss, yet not be detrimental to risk factors for chronic diseases.

The diet recommended by the Prostate Cancer Foundation (PCF) includes consumption of a variety of fruits and vegetables, specifically mentioning "colorful fruits and vegetables", which would signify carotenoid content. The PCF also recommends the inclusion of vegetables without specific frequency from the cruciferous family (cabbage, cauliflower, broccoli, kale, etc.), which contain glucosinolates, a phytonutrient family with strong cancer protection [5]. The PCF recommends reducing foods high in fat, however, carotenoids need dietary fat to be absorbed and transported [6] [7] and glucosinolates are water soluble and are lost in water based preparation (boiling, streaming) [8], but may be preserved when cooked in fat. Effective dietary advice for decreasing prostate cancer risk and progression should include healthy fat to prepare the cancer protective vegetables to maximize the absorption of carotenoids and possibly the glucosinolates.

Extra virgin olive oil may be unique in decreasing the risk of a number of cancers [9], including prostate cancer. Specifically, men in Greece and Spain consuming a traditional olive oil enriched Mediterranean diet have low rates of prostate cancer [10]. Plant-based diets that include olive oil may also increase vegetable intake relative to lower fat diets [11] [12] possibly due to the improvement in taste of the vegetables.

The objectives of this study was to compare the diet recommended by the PCF to a plant-based, olive oil diet developed by the PI in men with prostate cancer on surveillance or who have had an asymptomatic biochemical failure after primary therapy for weight loss and improvement in metabolic biomarkers (specifically fasting insulin and glucose). The secondary objectives were to test which diet will be more acceptable for long term use and if more specific diet recommendations for vegetables would influence vegetable intake.

## 2. Materials and Methods

Subject recruitment: Men diagnosed with prostate cancer on active surveillance, or have had an asymptomatic biochemical relapse after primary therapy with surgery or radiation, from a Multidisciplinary Genitourinary Oncology Lifespan Clinic were offered study participation. All appointments took place at the Lifespan Hospital facilities. Men on surveillance met the following criteria: Gleason scale of <6; PSA < 10 ng/mL; clinical stage T1c or T2a;  $\leq$ 3 positive cores; all biopsy cores were <50% involvement. Men classified as biochemical relapse on surveillance met the following a na-

dir; received primary treatment for prostate cancer; PSA < 10 ng/mL no radiographic evidence of metastatic disease. Qualifying Body Mass Index (BMI) was  $\geq$  25.0 (overweight)  $\leq$  40.0 kg/m<sup>2</sup> (obesity up to class 3 obesity).

Diets compared: 1) PCF diet; and 2) plant-based, olive oil diet, developed by the study PI. Participants consumed each diet for 8 weeks of weight loss with random assignment by number to the order. The study PI, a research dietitian, generated the random number assignment and provided all the dietary instruction. Due to the differences in diets, the assignment was not blinded. They were given a weight loss goal of 5% loss from baseline weight to end of study. After consuming the diets, participants will be asked to select one of the diets for an additional six months of follow-up.

Prostate Cancer Foundation diet: The PCF diet guidelines are to include nine servings of fruits and vegetables a day with an emphasis on colorful fruits and vegetables; include cruciferous vegetables; avoid charred meat; limit sugar intake; decrease carbohydrate intake; increase protein intake; limit high fat foods. The dietary fat allowed was any vegetable seed oils, *trans* fatty acid-free margarine, commercial salad dressings and mayonnaise. They were told not to consume extra virgin olive oil during this diet. All dairy foods were low/nonfat. Poultry/seafood/lean red meat intake were not limited.

Plant-based, olive oil diet: while on this diet, participants had a daily goal of 3 tablespoons of extra virgin olive oil (provided: Cobram Estates, Lara, Australia; robust variety; total phenol content = 625 mg/kg); nuts and olives were also allowed. Other oils and products made with them were proscribed. A maximum of 8 oz. of poultry or seafood/ day was allowed. Participants were asked to eat beef no more than once per month.

For both diets, they were instructed to emphasize vegetable intake, as studies indicate vegetable intake may be more protective for prostate cancer compared to fruit [13] [14]. While emphasizing vegetable intake over fruit intake, the PCF diet instruction adhered to the PCF guidelines to incorporate colorful vegetables and fruit and to include cruciferous vegetables and processed tomato products. Diet instruction for the olive oil diet was more specific to test if this would increase vegetables that the literature suggests are more protective. While on the olive oil diet, participants were given a goal of at least five servings a day of vegetables and four servings of fruit with an emphasis on colorful produce, a goal of at least 1 serving per week of cruciferous vegetables, as weekly intake has shown to be the level related to a decrease risk of risk of prostate cancer risk [15] and progression [16]. While on the olive oil diet participants were also instructed to include at least two servings a week of processed tomato products as processed tomatoes have the more bioavailable lycopene [17]. Throughout each diet, the participants were allowed up to two drinks of alcohol per day as this is the upper limit that is not related to increasing risk of prostate cancer [18].

Participants daily recorded their intake for type and amount of dietary fat, fruits, vegetables, processed tomatoes, cruciferous vegetables, and meat/poultry/ seafood during each eight weeks of diet. Participants were provided with postage paid envelops to return the daily records at the end of each week. The records were reviewed by the study PI for adherence to the diet and participants were called to verify the data and to provide any needed diet adjustment to ensure participant was eating the diet prescribed. Those whose records did not reflect the diet prescribed had the correct diet prescription reinforced. Those who would not follow the diet after at least two weeks of encouragement were removed from the study; no data from those discontinuing the study was used. During the six months of follow-up the daily food record was kept for one week per month. In addition, participants kept a three-day diet diary during weeks 4 and 8 of each diet and at the end of three and six months of follow-up. The three-day diet diaries were analyzed with iProfile 3.1, John Wiley & Sons, Inc. for energy and macronutrients (2016).

After completing the two eight weeks of each diet, participants were asked to select one of the diets for six months of additional weight loss or weight maintenance. For those selecting the olive oil diet, the extra virgin olive oil was not provided and they were asked to use at least two tablespoons a day as part of their meals as that is the minimum amount needed for the health benefits [19] [20]. They were provided with advice on brands of extra virgin olive oil to purchase to better ensure they were using extra virgin olive oil.

Study appointments were at baseline, after four and eight weeks of each diet and again after six months of follow-up. At all appointments, participants had their height and weight measured. Fasting blood samples were collected during weeks eight and after the last day of each diet, and again after six months of follow-up. The blood was analyzed on the day the sample was provided for totaland high density lipoprotein (HDL)-cholesterol, triglycerides, insulin, and glucose using standard clinical laboratory procedures. Low-density lipoprotein cholesterol (LDL-c) will be calculated using standard calculation. Homeostatic model assessment (HOMA) was calculated (glucose  $\times$  insulin/22.5). Olive oil analysis was by Modern Olives Laboratory Services in Lara, Australia using the method COI/T.20/Doc No 29 (2009). Determination of polyphenols in the olive oil was by HPLC.

Statistical analysis: The values of the two samples after each eight weeks of diet were averaged to receive a mean value that represented the response to the diet. The primary outcomes were to compare the diets for weight loss and improvement in insulin and glucose. The secondary outcomes were to compare the diets for acceptance and differences in vegetable intake. Paired t-tests were used to compare the data.

The study was approved by the Institutional Review Board at The Miriam Hospital, Providence, RI. All participants gave written informed consent.

### 3. Results

Recruitment took place from January 2015 through January 2016. This was a pilot study with 12 months of funding. Thirty men entered the protocol. Twelve

dropped out, 11 due to diet compliance. Five of the nine of the drop outs during the PCF diet were because they had consumed the olive oil diet first and were not willing to stop using extra virgin olive oil, which was required to continue in the protocol. Three who started with the PCF diet would not eat sufficient daily produce while on the PCF diet. One participant dropped out due to family issues. Three were removed from the olive oil diet for not consuming three tablespoons of extra virgin olive oil daily. The eighteen who completed the two diets had a baseline mean age of  $66.6 \pm 5.9$  years and a BMI of  $30.9 \pm 2.7$  kg/m<sup>2</sup>.

**Table 1** has the weight loss and laboratory comparisons by diet. While triglycerides were not significantly lower for the group after the plant-based, olive oil diet, 10 of the 18 had lower values after the olive oil diet.

**Table 2** has the dietary intake data. Despite similar weight loss on the diets, the participants reported consuming more total energy while on the on olive oil diet. Although beef consumption was lower on the olive oil diet, six of the 18 reported consuming beef more than twice. The mean reported daily extra virgin olive oil was  $2.9 \pm 0.3$  tablespoons.

Follow-up: Fourteen of the 18 eligible for follow-up chose the olive oil diet. One of these dropped out in the first month of the follow-up olive oil diet due to a change in employment. **Table 3** has the comparison of the body weight and labs after 6 months of FU for the thirteen completing follow-up to their values at the beginning of FU. The improvements achieved after the two weight loss diets were maintained after 6 months of the plant-based, olive oil diet. Eleven of these 13 had lost at least 5% of their baseline weight by the end of the 6 months of follow-up.

#### 4. Discussion

The PCF diet and the plant-based, olive oil diet produced similar weight loss in an eight week comparison, yet the participants reported a higher energy intake on the diet that included olive oil. This anomaly was also seen in previous com-

Variable	Olive oil	PCF	<i>P</i> =
Weight loss (%)	$2.8 \pm 3.7$	$2.5 \pm 3.1$	0.86
Total cholesterol (mmol/L)	$4.21\pm0.71$	$4.19\pm0.76$	0.65
LDL (mmol/L)	$2.5\pm0.64$	$2.43\pm0.78$	0.29
HDL (mmol/L)	$1.18\pm0.35$	$1.15\pm0.36$	0.12
Triglycerides (mmol/L)	$1.01\pm0.48$	$1.16\pm0.70$	0.18
Insulin (mU/L)	$79.87\pm30.56$	$95.15\pm48.62$	0.02
Glucose (mmol/L)	$5.5 \pm 0.53$	$5.82 \pm 0.55$	0.01
HOMA-IR	$19.5\pm0.72$	$24.6\pm1.2$	0.02

Table 1. Weight loss and laboratory values after diets.

mean ± SD. Abbreviations: Olive oil: plant-based, olive oil diet; PCF: Prostate Cancer Foundation diet; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; FBG: fasting blood glucose; HOMA: homeostatic model assessment.

	Olive oil	PCF	<i>P</i> =
Kjoules	8015.6 ± 2018.4	60033.6 ± 1997.5	< 0.00
Carbohydrate (g)	$224.9\pm79.8$	$189.1 \pm 74.2$	< 0.00
Fiber (g)	$29.8\pm8.8$	23.1 ± 6.7	< 0.00
Protein (g)	$71.5\pm19.9$	87.8 ± 22.1	0.01
Total fat (g)	$78.2\pm16.4$	$38.4 \pm 18.7$	0.00
Cholesterol (mg)	$210.5\pm130.7$	$293.5\pm121.0$	< 0.00
Total beef intake (oz).	$18.6\pm18.2$	$72.9\pm60.8$	<0.00
Veg + fruit/day (serv)	$8.2 \pm 1.8$	$8.2 \pm 1.6$	0.97
Vegetables/day (serv)	$5.5 \pm 1.5$	$4.4\pm1.4$	0.01
Dark vegetables/day (serv)	$3.4 \pm 1.2$	$2.2\pm0.9$	<0.00
Fruit/day (serv)	$2.6 \pm 1.1$	$3.8 \pm 1.7$	< 0.00
Dark fruit/day (serv)	$0.8\pm0.5$	$0.8\pm0.5$	0.94
Cruciferous/week (serv)	$7.6 \pm 7.4$	$6.5\pm6.7$	0.44
Processed tomato/week (serv)	$4.5\pm2.9$	$2.0 \pm 1.8$	< 0.00

Table 2. Diet data: 3-day diet diaries and daily sheets for key food items.

Mean ± SD. Abbreviations: olive oil: plant-based, olive oil diet; PCF: Prostate Cancer Foundation diet.

Table 3. Comparing val	lues after comp	eletion of both	diets to values	after 6-month	ns of fol-
low-up (n = 13).					

Variable	Baseline of FU	Post 6 months FU	P =
Weight (kg)	$89.7\pm8.0$	87.9 ± 6.7	0.97
Total cholesterol (mmol/L)	$155.7 \pm 31.7$	$164.5 \pm 33.9$	0.18
LDL (mmol/L)	96.0 ± 28.9	$104.9\pm30.5$	0.16
HDL (mmol/L)	46.5 ± 13.1	46.1 ± 11.9	0.77
Triglycerides (mmol/L)	75.9 ± 25.9	$75.8 \pm 18.4$	0.97
Insulin (mU/L)	$11.9 \pm 5.6$	$11.1 \pm 2.2$	0.62
FBG (mmol/L)	$100.4\pm9.7$	$101.2 \pm 13.9$	0.75
HOMA-IR	3.0 ± 1.5	$2.8\pm0.7$	0.65

 $mean \pm SD. \ Abbreviations: \ LDL: \ low-density \ lipoprotein \ cholesterol; \ HDL: \ high-density \ lipoprotein \ cholesterol; \ FBG: \ fasting \ blood \ glucose; \ HOMA-IR: \ homeostatic \ model \ assessment.$ 

parisons of the olive oil diet to lower fat diets [11] [21]. Despite the similar weight loss and higher energy intake, the diet that included extra virgin olive oil resulted in lower levels of fasting glucose, insulin and HOMA. The olive oil diet was overwhelmingly preferred for follow-up. In addition, five participants who started on the olive oil diet would not discontinue their daily olive oil intake to enter the PCF diet phase, indicating a preference for the diet that included daily olive oil. The olive oil diet also resulted in higher total and deep-colored vegetable and processed tomato intake.

This protocol was based on an earlier pilot study by the PI that compared the

National Cancer Institute diet for women with breast cancer to the same plant-based, olive oil diet [11]. In that study, however, weight loss was greater on the olive oil diet compared to the lower fat diet. As seen in the current study of men, more women in the earlier study chose the olive oil diet for six months of follow-up. Weight loss does not differ by nutrient content of the diet, but is improved with diet adherence [4], thus a diet that includes extra virgin olive oil may improve long term body weight.

Both fasting glucose and insulin were lower after the diet that contained extra virgin olive oil. Compared to vegetable seed oil, extra virgin olive oil has been show to produce lower levels of both glucose and insulin [22] and decrease insulin resistance [23]. As there is a positive relationship of fasting insulin to prostate cancer development [24] and both blood glucose and insulin resistance are positively related to cancer mortality [25] [26], daily consumption of extra virgin olive oil may help improve survivorship for cancer. It was anticipated that the diet that included extra virgin olive oil would also improve triglycerides. However, this improvement was not realized for the group but the majority of the participants had lower triglycerides after the diet that included extra virgin olive oil.

The PCF recommends reducing high-fat foods [27], however extra virgin olive oil may have a unique role in a diet prescription for cancer patients. Populations who naturally use extra virgin olive oil as their primary fat have lower risk of several cancers [9]. There are a number of components in extra virgin olive oil that could explain the relationship to decreasing cancer risk. As it is primarily monounsaturated fat, olive oil does not contribute to oxidation. If the health benefits of olive oil were due to the monounsaturated fat content, extra virgin olive oil would be interchangeable with refined olive, and even canola oil. Studies show that extra virgin olive oil has components beyond monounsaturated fat that are not present in refined olive oil or canola that could decrease cancer risk. It is the oil with the highest content of alpha -tocopherol, the antioxidant form of vitamin E [28]. It contains phenolic antioxidants, including simple phenols (hydroxytyrosol, tyrosol), flavonoids, and lignans [29]; and squalene [30], which has been shown to be a tumor inhibitor [31], and thought to be largely responsible for decreasing cancer risk [31] [32].

An objective of this study was to test if the participants would improve their consumption of certain vegetable types by providing weekly goals. While on the PCF diet they were instructed to consume nine servings a day of colorful fruits and vegetables and to include cruciferous vegetables, which is the advice of the PCF. Vegetable consumption was emphasized for both diets as studies indicate vegetable intake may be more protective for prostate cancer compared to fruit [13] [14]. The diet instruction for the olive oil diet included a goal of at least five servings a day of vegetables. While the combined vegetable plus fruit intake did not differ between the diets, the distribution differed with more vegetables being consumed on the olive oil diet and more fruit on the PCF diet. For the olive oil

diet, they were given a goal of at least one serving per week of cruciferous vegetables, as one to two servings a week of cruciferous vegetables has been related to decreasing prostate cancer risk by more than 30% [15] [33] [34], and decreasing the risk of prostate cancer progression by more than 50% [33]. The intake of cruciferous vegetables did not differ between the diets and on both diets the average intake was six or more servings per week.

The olive oil diet resulted in a higher intake of dark vegetables, despite the advice for both diets to emphasize dark produce, so this difference was not anticipated. The deep pigment in plant products is due to the carotenoid content, which have been shown to have powerful cancer protective properties [35]. As carotenoids need dietary fat present to be maximally absorbed and transported [6] [7], the increased intake of dark vegetables on the diet that included olive oil would be especially healthy. The dietary advice for both diets included the weekly consumption of processed tomato products due to the form of lycopene in processed tomatoes. Lycopene is the carotenoid most related to improving prostate cancer risk; however, not all studies of lycopene intake have shown a benefit. Processing lycopene containing foods at high temperature (*i.e.*, canning) converts the lycopene to the *cis* form, which has a much higher bioavailability than the *trans* form [17] found in fresh tomato. Participants reported consuming more processed tomatoes while on the olive oil diet, this also was not anticipated.

Strengths: The extra virgin olive oil used in the study was provided in the eight week diet comparison to ensure the authenticity of the oil. The men were recruited by a nurse practitioner and physician from their practice so the participants were known by the staff. The keeping of daily food records helped to know what the participants were eating and if they were following the diets as prescribed.

Limitations: This study reports on 18 participants and a larger number would be needed to determine if the results can be replicated with a larger sample of patients with prostate cancer. Also, a longer time period of comparison may be useful, but the eight weeks was selected as it is sufficient to see for weight loss to occur and for the participant to have sufficient time to evaluate the diet, but not too long if they found the diet undesirable. The olive oil was not provided during the six months of follow-up to see if the participants were willing to purchase extra virgin olive oil for home use, however, the participants were provided with information on purchasing of extra virgin olive oil to make sure they were using an acceptable olive oil. The assignment could not be blinded due to the differences in diet.

## **5.** Conclusion

Both the diet recommended by the PCF and a plant-based, olive oil diet could be used by men with prostate cancer on surveillance for weight loss, but the diet that included daily extra virgin olive oil may lead to better weight management long-term. The daily use of extra virgin olive oil, should also improve fasting glucose and insulin levels, which should improve survival. In addition, dietary advice to include extra virgin olive oil could increase vegetable intake and blood levels of cancer-protective carotenoids. Further study with additional participants would show if the results seen here will be replicated.

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