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# Do New Zealand men with prostate cancer benefit from a Mediterranean-style diet?

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Carcinoma of the prostate is the most commonly diagnosed malignancy and the third leading cause of mortality in New Zealand men, making it a significant health issue in this country. Global distribution patterns suggest that diet and lifestyle factors may be linked to the development and progression of this cancer. Twenty men with diagnosed prostate cancer adhered to a Mediterranean diet, with specific adaptations, for three months. Dietary data, prostate-specific antigen, C-reactive protein and DNA damage were evaluated at baseline after three months of following the diet. A significant reduction in DNA damage compared to baseline was apparent, with particular benefit noted for overall adherence to the diet ( $p = 0.013$ ), increased intake of folate ( $p = 0.023$ ), vitamin C ( $p = 0.007$ ), legumes ( $p = 0.004$ ) and green tea ( $p = 0.002$ ). Higher intakes of red meat and dairy products were inversely associated with DNA damage ( $p = 0.003$  and  $p = 0.008$  respectively). This small study demonstrated that a high-antioxidant diet, modelled on Mediterranean traditions, may be of benefit for men with prostate cancer. Protection against DNA damage appears to be associated with the diet implemented, ostensibly due to reduction in reactive oxidant species. These findings warrant further exploration in a longer trial, with a larger cohort.

# Do New Zealand Men with Prostate Cancer Benefit from a Mediterranean-Style Diet?

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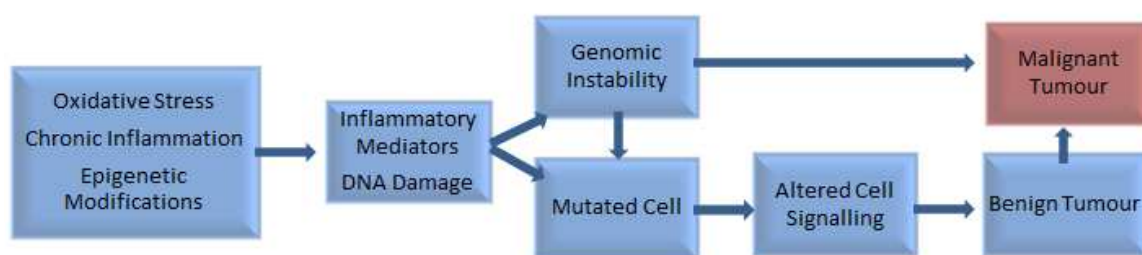
## Introduction

On a global scale, prostate cancer is an important health consideration. It is the fourth most common cancer internationally, and in men ranks second only to lung cancer (Ferlay et al., 2012). Prostate cancer incidence is highest in developed nations, compared to less-developed countries, a difference that is only partially explained by the higher use of prostate specific antigen (PSA) as a screening tool in developed nations (Center et al., 2012). In New Zealand, cancer of the prostate is the third most common cause of cancer-related mortality, with death rates disproportionately higher in Māori men (28.7 c.f. 16.7 deaths per 100,000 (age-standardised rates per 100,000 male population, standardised to the WHO world standard population) ("Cancer: New registrations and deaths 2010," 2013).

Worldwide patterns of prostate cancer incidence and mortality support the hypothesis that diet and lifestyle are likely contributors to both development and progression of this malignancy. Furthermore, alterations in risk associated with migratory patterns and the westernisation of dietary patterns associated with globalisation (Baade, Youlden & Krnjacki, 2009; Melnik, John & Schmitz, 2011) give added credence to this theory.

Both family history of the disease and advancing age are known risk factors (Center et al., 2012), yet the pathogenesis of prostate cancer is not well understood. Chronic inflammation and infection have been implicated in the development of around one-fifth of all cancers (Greene et al., 2011), including prostate cancer (Gurel et al., 2014). Other influences include genetic and epigenetic factors (Pantuck et al., 2006), imbalances between reactive oxygen species and antioxidants, and DNA damage (Waris & Ahsan, 2006)(Figure 1).

**Figure 1.** Factors involved in the pathogenesis of tumour development (Pantuck et al., 2006; Waris & Ahsan, 2006).



The role of inflammation in prostate cancer is unclear. Elevated levels of inflammatory markers have been associated with high-grade prostate cancer in some studies (Shariat et al., 2001; Platz & De Marzo, 2004; Huffman et al., 2006; Gurel et al., 2014) but not in others (Il'yasova et al., 2005; Stark et al., 2009). Systemic inflammation has been associated with earlier cancer mortality (McArdle, Qayyum & McMillan, 2010; Shafique et al., 2012), which adds weight to an argument for a detrimental effect of chronic inflammation and the potential benefit of a low-inflammatory diet.

Increased levels of free radicals and pro-oxidant compounds (Arsova-Sarafinovska et al., 2009; Qu et al., 2013; Kanwal et al., 2014), and decreased levels of antioxidant enzymes have been found in prostate tissue (Kanwal et al., 2014), and in association with prostate cancer (Arsova-Sarafinovska et

al., 2009). Both prostatic cancer cells and high-grade prostatic intraepithelial neoplasia are notably deficient in the important endogenous antioxidant, glutathione *S*-transferase (Platz & De Marzo, 2004). This may be due to inflammation-induced inactivation of genes that have roles in cellular protection and restoration of damaged DNA (Kundu & Surh, 2012). Reduction in the ability of cells to produce protective antioxidants may occur due to alterations in cell morphology, leaving the prostate vulnerable to damage by carcinogenic compounds that might otherwise be neutralised by antioxidants. Indeed, proliferative inflammatory atrophy, a precursor to development of prostate cancer, is a cellular change that is postulated to be the result of cell damage (Platz & De Marzo, 2004; Brawer, 2005).

The Mediterranean diet has been extensively examined and its benefits in terms of reductions in oxidative stress and inflammation are generally well-accepted (Urpi-Sarda et al., 2012; Viscogliosi et al., 2013). This dietary style is centered on consumption of high amounts of extra virgin olive oil, fruit and vegetables, pulses and legumes, whole-grains, and poultry, along with some fish and seafood. Intake of red meat, dairy products and processed or refined foods is traditionally low (Couto et al., 2011). Deviation away from such a pattern, towards a more western-style diet, has been associated with increased prostate cancer incidence (Ambrosini et al., 2008; Stott-Miller, Neuhaus & Stanford, 2013). Couto *et al.* (Couto et al., 2011) examined data from the large European Prospective Investigation into Cancer and Nutrition (EPIC) study and concluded that a Mediterranean diet is particularly beneficial in protecting against breast, colon, and prostate cancer. Analysis of individual components of the diet did not provide convincing data; it was the overall dietary pattern that appeared to confer protection. The level of benefit was positively correlated to how closely the diet was followed. This was also demonstrated in a recent study in which adherence to a Mediterranean-style diet was associated with lower prostate cancer mortality (Kenfield et al., 2014).

The brassica family is not emphasised in general Mediterranean diet guidelines. However, this family of vegetables has attracted much interest in recent years, primarily on account of the levels of glucosinolates, which are particularly high in broccoli (Moreno et al., 2006). Nutrigenomic effects of broccoli are discussed in detail in Ferguson and Schlothauer (Ferguson & Schlothauer, 2012).

Pomegranate, and its juice, has received a great deal of attention related to potential chemo-protective effects, including beneficial effects in slowing of prostate-specific antigen (PSA) doubling time in men with prostate cancer (Pantuck et al., 2006, 2009; Paller et al., 2012). This benefit is attributed to high levels of polyphenols (particularly punicalagin, an ellagitannin (Koyama et al., 2010)), that contribute to pomegranate's overall antioxidant capacity, which is greater than either red wine or green tea (Gil et al., 2000). Polyphenols are also high in extra virgin olive oil, red wine, and green tea (Tuck & Hayball, 2002). These phytochemicals have demonstrable epigenetic effects (Joven et al., 2013), which may account for at least some of the benefits attributed to their consumption. As pomegranate is found throughout the Mediterranean area, it is logical to assume it would be commonly consumed in the region. However, this has not been reported in nutritional research which focuses on Mediterranean dietary patterns. It is quite possible that pomegranate may be a contributor to documented advantages associated with diets in the Mediterranean region.

High fibre diets, including consumption of legumes and whole grains, have been linked to a wide range of health benefits. Legumes are an important food group in the Mediterranean diet (Ferris-Tortajada et al., 2012), and have been associated with reduced prostate cancer risk (Chan, Lok & Woo, 2009). Consumption of legumes (particularly soy) is significant in Asian diets where prostate cancer

incidence is also low (Chan, Lok & Woo, 2009). Mechanisms for benefit are numerous and include: high fibre content, which may be advantageous by reduction of post-prandial glycaemia (Gropper, Stepnick & Smith, 2013), lower levels of insulin-like growth factor (Landberg et al., 2010), and increases in sex hormone binding globulin (Tymchuk et al., 1998). The minimisation of post-prandial rises in blood sugar level is desirable in men with prostate cancer, due to glycaemia-associated increases in markers of inflammation and oxidative stress (Rytter et al., 2009). Additionally, foods that promote a high glycaemic response induce insulin and insulin-like growth factor (Melnik, John & Schmitz, 2011), which may contribute to prostate cancer progression (Chan et al., 2002).

In some studies (Gao, LaValley & Tucker, 2005; Koh et al., 2006; Allen et al., 2008), but not all (Huncharek, Muscat & Kupelnick, 2008; Pettersson et al., 2012), consumption of dairy foods has been linked to higher risk of developing prostate cancer. Risk has been associated with the quantity consumed (Allen et al., 2008) and dairy intake during adolescence (Torfadottir et al., 2012). Prostate cancer mortality has also been correlated to milk consumption (Ganmaa et al., 2002). While these data are inconclusive, it does, nonetheless, raise concerns over the recommendation of dairy as a source of calcium for men at risk of developing osteoporosis, including those with prostate cancer who have had hormonal ablation treatment (Malcolm et al., 2007).

Fish is not considered a major component of Mediterranean diets (Trichopoulou et al., 2005), but is generally considered preferential to red meat for men with prostate cancer (Terry et al., 2001; Chavarro et al., 2008; Bosire et al., 2013). Fish is regarded as a good source of omega-3 polyunsaturated fatty acids, promoting anti-inflammatory pathways (Jain et al., 2008), which has been considered to be desirable in men for whom lowering inflammation is a goal. However, the benefit of omega-3 polyunsaturated fatty acids in prostate cancer has recently been challenged (Brasky et al., 2013). The role of dietary fats in prostate cancer is discussed in more detail by Bishop, *et al* (Bishop et al.).

Green tea is not a dietary feature in the Mediterranean region, but is a common beverage in East Asian countries, where mortality rates from prostate cancer are the lowest, globally (Ferlay et al., 2012). A mounting volume of evidence supports the recommendation of consumption of green tea, due to its antioxidant potential, largely from polyphenols, in particular epigallocatechin-3-gallate (EGCG) (Du et al., 2012). EGCG has documented anti-proliferative properties (Du et al., 2012) and affords protection to DNA in prostate cells (Kanwal et al., 2014). Furthermore, green tea consumption has been associated with lower prostate cancer incidence (Zheng et al., 2011) and reduced risk of progression to advanced disease (Kurahashi et al., 2008).

This study was undertaken to establish the likely benefit of three months of adherence to a Mediterranean dietary pattern, with specific modifications, on DNA damage and inflammation in New Zealand men with prostate cancer.

## Materials and Methods

Written approval for this study was granted by the Northern Y Regional Ethics Committee (New Zealand), study reference NTY/11/11/109.

Study participants with Gleason score 6 – 7 (3 + 3 or 3 + 4) who had participated in an earlier study consented to participation and were enrolled. Other criteria for inclusion were: under 75 years of age, no diagnosis of diabetes, stable prostate cancer, not currently receiving treatment for prostate cancer (hormonal therapy excepted), and with no current other cancer.

Men were given nutritional counselling, dietary guidelines, and a comprehensive collection of recipes (Erdrich & Bishop, 2013) which incorporated the main foods and principles of the diet. New Zealand-produced olive oil (polyphenol level 233 mg/kg), salmon (200 g/week), pomegranate juice (1 L per week) and samples of canned legumes were supplied by our New Zealand sponsors: Oil Seed Extractions Ltd., Ashburton; Aoraki Smokehouse Salmon, Twizel; Life Juices, Auckland, and Delmaine Fine Foods, Auckland, respectively.

Blood samples were collected at baseline, and again at three months of follow-up, (plain, EDTA, Heparin and SST II Advance Vacutainers), and processed within 2 h of collection. C-reactive protein and PSA were tested using enzyme immunoassay by LabTests, Auckland, New Zealand.

Comet assays were performed on both fresh blood and hydrogen-peroxide challenged samples as described by Karunasinghe *et al* and Ferguson *et al* (Karunasinghe *et al.*, 2004; Ferguson *et al.*, 2010). As the data were skewed, figures for percentage tail DNA were log-transformed and the back-transformed mean was used for the analysis.

Study participants completed dietary adherence questionnaires and four-day diet diaries at the beginning and conclusion of the study. Diet diaries were analysed using FoodWorks<sup>®</sup>7 (Xyris 2012, Xyris Software (Australia) Pty Ltd, Brisbane, Australia).

Statistical evaluation was performed using SAS (v9.2 SAS Institute, Cary, NC, USA). Correlations were examined using Spearman's rho. The Student's paired *t*-Test was used to evaluate differences between baseline and study-end.

## Results

A total of twenty-eight men were enrolled in the study. Eight men were not included in the final analysis: four were lost to follow-up for a variety of reasons, two dropped out of the study due to life stresses, one had difficulty conforming to the diet and one was eliminated due to unreliability of dietary information provided. The characteristics for the remaining twenty participants are presented in Table 1.

**Table 1.** Characteristics of study participants at baseline.

Characteristic	<i>n</i>	Characteristic	<i>n</i>
Age 52–74 Years		BMI 23–33 kg/m <sup>2</sup>	
50–59	3	≥20–≤25	4
60–69	12	>25–≤30	12
>70	5	>30	4
Marital Status		Family History of PCa	
Married or with Partner	17	1° relative with PCa	3
Single or Widowed	3	Other relative with PCa	2
Ethnicity		Gleason Score	
Caucasian	20	3 + 3	14
Smoking Status		3 + 4	6
Never	7	Treatment type	
Former	13	None	6
Current	0	Prostatectomy	10
Activity Level *		Prostatectomy + Hormones + DxR	1
Heavy	1	Prostatectomy + DxR	1
Moderate	2	Hormones + DxR	1



Light-Moderate	1	Brachytherapy	1
Light	5	Medication	
Sedentary	10	Statins	6
Very Sedentary	1	Aspirin	5
Alcohol Intake		Diclofenac	4
Non-Drinkers	4	Anti-hypertensive	4
≤2 Standard Drinks Per Day	10	TNF-antagonist	1
>2 Standard Drinks Per Day	6	Allopurinol	1
PSA (mean, µg/L)	1.53	Other	6
CRP (mean, mg/L)	1.55		

BMI, body mass index; 1°, first degree; PCa, prostate cancer; DxR, radiotherapy; PSA, prostate-specific antigen; CRP, C-reactive protein; \* Physical activity level as defined by FoodWorks<sup>®</sup> 7.

Of the twenty participants in the final analysis, none were current smokers. Mean time since smoking cessation was 31 years (SD 13). Past history of smoking of less than one pack-year was regarded as a “never-smoker”. Pack-year history was positively associated with the use of Aspirin and/or Diclofenac ( $p = 0.007$ ).

Over the course of the study two men ceased taking and one commenced low dose Aspirin. Another participant discontinued use of Diclofenac during the study period.

Of this somewhat sedentary group of men, 70% were overweight or obese ( $\text{BMI} > 25 \text{ kg/m}^2$ ); mean body weight reduced by 2.3 kg (95% CI 1.11–3.49,  $p < 0.001$ ), over the course of the study. There was a mean reduction in body mass index of  $0.85 \text{ kg/m}^2$  (95% CI 0.52–1.18,  $p < 0.001$ ).

Men who were less active tended to have higher levels of C-reactive protein ( $p = 0.003$ ). This association remained at study end, albeit slightly weaker ( $p = 0.055$ ).

At baseline, dietary scores for the targeted Mediterranean-style pattern were low. Mean adherence was 6.3 (SE 0.69), with individual scores ranging from 2 to 13 (of a maximum of 20). At three months of follow-up, mean adherence was 13.63 (SE 0.49), range 9 to 17. The mean change in dietary adherence from baseline to study end was +7.33 (95% CI 5.76–8.89), which was highly significant ( $p < 0.001$ ).

There were no statistically significant relationships between dietary adherence and either C-reactive protein or PSA at either baseline or three months.

Improvements were noted in all areas evaluated on the adherence questionnaire, with the exception of servings of fruit, vegetables, use of *sofrito* (tomato-based sauce prepared with garlic and/or onion), the intake of sweetened beverages, and wine. Pooled group adherence scores are presented in Table 2.

**Table 2** Pooled dietary adherence scores from 20 participants at baseline and three months. A maximum of 1 point for each item per participant was possible. 20 points reflects complete adherence by the whole cohort.

Dietary Component	Criteria for One Point	Baseline	Three Months *	$p$
1. Olive Oil As Culinary Fat	Yes	13	20.0	<b>0.021</b>
2. Olive Oil Used Daily	$\geq 1$ tblsp	8	17.0	<b>0.003</b>
3. Servings of Vegetables/Day	$\geq 4$	6	8.5	0.0563
4. Servings of Fruit/Day (Incl. Pomegranate)	$\leq 2$	9	11.5	0.449
5. Servings of Red Meat, Hamburger, etc./Week	$< 1$	1	11.5	<b>&lt;0.001</b>
6. Servings of Butter, Margarine or Cream/Day	$< 1$	3	14.5	<b>&lt;0.001</b>



7. Sweet or Carbonated Beverages/Day	<1	16	20.0	0.083
8. Wine Consumed/Week (Glasses)	7–14	5	5.5	0.577
9. Servings of Legumes/Week	≥5	6	16.0	<0.001
10. Servings of Fish or Shellfish/Week	≥3	4	14.0	<0.001
11. Sweets or Pastries/Week	<3	7	16.0	<0.001
12. Servings of Nuts/Week	≥5	5	16.0	<0.001
13. Preference for Chicken, <i>etc.</i>	Yes	7	18.0	<0.001
14. Use of <i>Sofrito</i> Sauce/Week	≥2	6	9.5	0.297
15. Servings of Pomegranate/Day	≥1	1	19.5	<0.001
16. Units of Other Alcohol (Excl. Wine)/Week	0	5	7.5	0.025
17. Cups of Green Tea/Day	≥2	2	9.0	0.008
18. Servings of Broccoli/Week	≥5	0	6.5	0.004
19. Servings of Dairy Products/Week	≤5	5	13.0	0.003
20. Use of Whole Grains	Yes	16	20.0	0.042

\* Half-points were allocated wherever a shift towards improved adherence of ≥30% was evident; tblsp, tablespoon; incl, including; excl, excluding.

Estimated energy requirements and reported energy intake were calculated using FoodWorks<sup>®</sup>7 software, from recorded body weights, reported energy expenditure and diet diaries (Table 3). There was a tendency to under-report energy intake. This was not statistically significant at baseline (SE 280, 95% CI 108–1063,  $p = 0.10$ ). At the end of the study period, the difference reached statistical significance, with reported energy intake a mean 720 kilojoules lower than estimated requirements (SE 194, 95% CI 314–1125,  $p = 0.007$ ).

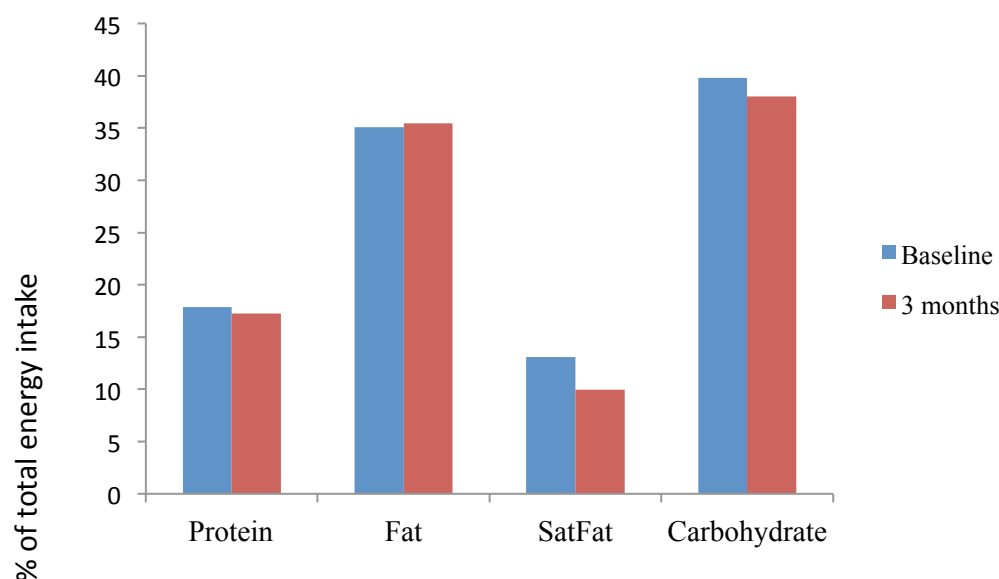
**Table 3** Comparison of estimated energy requirements and reported energy intake.

Energy Intake	Baseline Mean (SE)	Three Months Mean (SE)	Mean Difference (95% CI)	<i>p</i> - value
EER /kJ	10,675.6 (305.43)	10,476.05 (292.00)	−199.6 (−427.40–28.27)	0.083
Reported energy intake /kJ	10,197.7 (341.64)	9756.43 (267.09)	−441.3 (−970.60–88.05)	0.098

EER, estimated energy requirement; kJ, kilojoules; SE, standard error; CI, confidence interval.

Energy obtained from saturated fat, as % of total energy intake, decreased significantly ( $p < 0.001$ ). Other sources of energy did not alter significantly over the course of the study (Figure 2).

**Figure 2.** Changes in sources of energy, as % of total energy intake at baseline and three months. SatFat = saturated fat; \*  $p < 0.001$ .



Increases in intake of broccoli, *sofrito*, and pomegranate juice were statistically significant, as was a decrease in refined carbohydrate intake (per reported intakes of sweetened beverages and baked goods) (Table 4). The reduction in carbohydrate intake was not significant. No change was observed in regards to intake of fruit, vegetables, dietary fibre, or total sugar. It was apparent that the source of dietary sugars shifted away from sucrose and lactose, towards fructose and glucose.

No relationship was seen between sugar intake and C-reactive protein.

Participants significantly reduced their consumption of red meat ( $p < 0.001$ ), and increased their intake of fish ( $p < 0.001$ ), and legumes ( $p = 0.005$ ). In spite of these alterations in sources of protein, there was no significant change in total protein intake (Table 5).

**Table 4.** Changes in intake of dietary items and nutrients, from baseline to three months.

Dietary Component	Baseline Mean (SE)	3 Months Mean (SE)	Mean Difference (95% CI)	<i>p</i>
Carbohydrate (total) (g/day)	246.53 (11.20)	234.91 (11.00)	-11.63 (-30.47-7.22)	0.212
Dietary fibre (total) (g/day)	31.23 (1.86)	32.28 (1.60)	1.04 (-1.83-3.92)	0.456
Sugar (total) (g/day)	108.14 (7.90)	110.86 (7.96)	2.72 (-11.32-16.75)	0.690
Glucose (g/day)	19.00 (2.28)	32.30 (2.97)	13.22 (7.30-19.20)	<b>&lt;0.001</b>
Fructose (g/day)	20.80 (2.40)	28.80 (2.80)	8.55 (2.80-14.30)	<b>0.006</b>
Sucrose (g/day)	35.30 (4.80)	24.8(3.50)	-10.56 (-17.75-1.37)	<b>0.026</b>
Lactose (g/day)	12.80 (1.53)	6.53 (1.17)	-6.28 (-9.70-2.80)	<b>0.001</b>
Folate (total) (µg/day)	537.00 (43.50)	564.00 (40.40)	27.00 (-31.00-85.40)	0.340
Vitamin C (mg/day)	133.60 (13.20)	169.40 (22.40)	35.90 (-1.03-72.80)	0.056
Vitamin E (mg/day)	18.60 (4.90)	26.53 (5.46)	7.94 (3.18-12.70)	<b>0.005</b>
Vegetables (serves/day)	2.80 (0.28)	2.63(0.31)	-0.18(-1.13-0.78)	0.705
Broccoli (serves/week)	1.58 (0.27)	2.42 (0.45)	0.84 (-0.19-1.49)	<b>0.014</b>
<i>Sofrito</i> sauce (serves/week)	1.53 (0.45)	2.40 (0.47)	0.88 (0.28-1.47)	<b>0.006</b>
Fruit* (serves/day)	2.78 (0.49)	2.50 (0.31)	-0.28 (-1.01-0.46)	0.440

Pomegranate (serves/day)	0.05 (0.05)	1.28 (0.16)	1.23 (0.86–1.59)	<b>&lt;0.001</b>
Sweetened beverages (serves/week)	0.51 (0.20)	0.15 (0.06)	–0.35 (–0.70–0.01)	<b>0.046</b>
Cakes and biscuits (serves/week)	4.38 (1.01)	2.05 (0.55)	–2.33 (–3.82–0.83)	<b>0.004</b>
Green tea (cups/day)	0.35 (0.17)	1.13 (0.30)	0.78 (–0.28–1.84)	<b>0.004</b>

g, grams; SE, standard error; CI, confidence interval; \* All fruit and fruit juice, including pomegranate.

**Table 5.** Changes in protein intake from baseline to three months.

Dietary Component	Baseline Mean (SE)	3 Months Mean (SE)	Mean Difference (95% CI)	<i>p</i>
Protein (g/day)	106.73 (5.52)	99.49 (4.99)	–7.24 (–17.32–2.85)	0.149
Red & processed meat (serves/week)	3.89 (0.48)	1.94 (0.36)	–1.95 (–2.59–1.32)	<b>&lt;0.001</b>
Fish (serves/week)	1.65 (0.20)	3.48 (0.46)	1.83 (0.91–2.74)	<b>&lt;0.001</b>
Legumes (serves/week)	2.37 (0.58)	3.78 (0.46)	1.41 (0.48–2.34)	<b>0.005</b>

SE = standard error, CI = confidence interval.

Alterations in dietary fats and associated relationships are discussed in detail in Bishop, *et al* (Bishop et al.).

Reductions in DNA damage were noted after three months of the dietary intervention. This did not reach significance for basal (fresh-blood) DNA damage ( $p = 0.075$ ), but was highly significant for peroxide-induced DNA damage ( $p = 0.009$ ).

Spearman bivariate correlation was used to identify relationships between DNA damage at study end and intake of the items specified on the adherence questionnaire and data generated from diet diaries. Overall, following the dietary pattern was inversely associated with DNA damage ( $p = 0.013$ ). DNA damage was also inversely associated with consumption of green tea and intake of legumes ( $p = 0.002$  and  $p = 0.004$  respectively), and positively associated with red meat intake ( $p = 0.007$ ). Intake of dairy products and margarine/butter/cream was also correlated with DNA damage at study end. These results are discussed in Bishop *et al.* (Bishop et al.). No significant relationships were noted between DNA damage and vegetable, fruit, or pomegranate intake.

An inverse association between DNA damage and vitamin C intake was apparent. This was weak at baseline ( $p = 0.098$ ), and became significant at study-end ( $p = 0.007$ ). Dietary folate intake at three months was inversely associated with hydrogen peroxide-induced DNA damage ( $p = 0.023$ ). Vitamin E intake, which increased significantly (Table 4), was inversely associated with both basal and peroxide-induced DNA damage at the end of the study. However, with  $p$ -values of 0.175 for each, these did not attain statistical significance.

There were no significant relationships between C-reactive protein, PSA and DNA damage. A non-significant trend towards a correlation between C-reactive protein and peroxide-induced DNA damage was observed ( $p = 0.156$  and  $p = 0.223$  at baseline and three months, respectively).

## Discussion

The primary goal of this pilot study was to establish both feasibility and likelihood of benefit, as determined by a reduction in inflammation and DNA damage, for New Zealand men with prostate cancer following a modified Mediterranean diet. We sought to enroll men with untreated prostate cancer; however, due to low numbers of volunteers, men with low Gleason (3 + 3 or 3 + 4) who had previously had treatment were included. It was anticipated that as our subjects had volunteered to participate in this intervention, they would be motivated, and thus amenable to changes that might be seen as advantageous in delaying disease progression. This was observed, and is consistent with what has been previously demonstrated in regards to cancer, motivation and dietary changes (Allen et al., 2008). It was anticipated that the dietary intervention would have demonstrable effects on DNA damage and C-reactive protein.

From the results, it appears that the adoption of such a dietary pattern is feasible in motivated men (Table 2). Not only were the changes, for the most part, embraced, but feedback from individual participants was encouragingly positive. The majority indicated that they enjoyed the new diet and were heartened by their weight loss. Study participants also reported improvements in overall energy and well-being, as well as positive effects on a range of other factors, including serum cholesterol, arthritic pain, and nocturia.

Adherence to a low inflammatory diet such as that used in this study may help to mitigate inflammation-associated increases in oxidative stress, genomic instability and damage to DNA (Kundu & Surh, 2012).

Inflammation was evaluated using C-reactive protein. However, this did not change over the course of the study. Noteworthy in this regard is that baseline C-reactive protein in this group was low, with 95% of the cohort within the normal range of <5 mg/L, leaving little room for improvement. An inverse association between C-reactive protein and physical activity levels that was noted at the outset of this study was not evident at study end. Improvements in C-reactive protein in the most sedentary participants, and/or reductions in overall activity levels in three men who experienced varying non-cancer-related health challenges during the study, are possible explanations. The effect of excess adiposity is an important consideration on the results seen. Obesity is a chronic, low-grade inflammatory state, which has been associated with both incidence and progression of prostate cancer (Ho et al., 2012). It was expected that study participants might lose weight by following the dietary recommendations, which is a documented effect of following a Mediterranean-style diet (Martinez-Gonzalez et al., 2012). This weight loss (mean 2.3 kg), while desirable in overweight men, may have masked any anti-inflammatory benefit of the diet. When stored adipose tissue is catabolised, the pro-inflammatory omega-6 fatty acid, arachidonic acid, tends to be liberated (Phinney et al., 1991). Thus true benefit in terms of lowering of inflammation might be best observed once body weight has stabilised.

C-reactive protein responds to a number of factors. Participants were not evaluated for injury or opportunistic infection at either the beginning or end of the study. While men retrospectively reported that they were “well” at the time of both blood draws, minor injuries or low-grade infections have the potential to increase acute phase inflammatory markers, C-reactive protein included. Similarly, study participants were not assessed for other factors that might impact C-reactive protein, such as sleep disturbances (Meier-Ewert et al., 2004) and recent food intake (Margioris, 2009; Farnetti et al., 2011).

Levels of PSA were largely unchanged over the course of the study. However, PSA was below the level of detection in the majority of study participants, as is associated with successful treatment for prostate cancer. The lack of change in PSA, particularly in those men who had not had treatment for prostate cancer ( $n = 6$ ), may indicate benefit in terms of PSA doubling time. This is best evaluated over a longer period of time.

Energy from carbohydrates accounted for less than 40% of total energy intake at study commencement, which is somewhat below the recommended 50%–55% in the New Zealand guidelines (MOH, 2003). Under-reporting of energy intake, such as occurred in this study (Table 3), is a common issue in nutritional research (Bingham et al., 1997). Reduction in lactose intake is congruent with the reported decrease in dairy products (discussed in Bishop, *et al.* (Bishop et al.)), which was one of the dietary modifications requested. Lower intake of sucrose and the increase in fructose and glucose, along with the reported decrease in fruit intake (Table 4), suggests that participants either did not include pomegranate juice in the fruit category on the adherence questionnaires, or that actual fruit intake was reported more accurately in the diet diaries. This is consistent with other research, in which diet diaries more closely correlate to actual dietary intake (Bingham et al., 1997). Total carbohydrate intake was not associated with any of the biomarkers tested.

There are many individual components of the Mediterranean diet that have been studied in regards to their effect on a number of health outcomes. The health advantages of a diet that is high in fruit and vegetables, ostensibly due to the diversity of nutrients, with high levels of antioxidants and fibre associated with such dietary patterns is generally accepted. Indeed, lower levels of inflammation and increases in antioxidants have been correlated to fruit and vegetable intake (Root et al., 2012). While not all studies concur (Ambrosini et al., 2007; Boffetta et al., 2010), there is evidence suggesting benefit from vegetable and fruit intake in regards to prostate cancer (Riso et al., 1999; Hardin, Cheng & Witte, 2011; Shahar et al., 2011).

The main benefit (weight loss aside) associated with this dietary intervention was reduction in DNA damage after three months, when compared to baseline data. This outcome was inversely associated with dietary adherence ( $p = 0.013$ ).

Three months is considered sufficient time to determine the impact of diet on DNA repair in lymphocytes. As part of the circulatory system lymphocytes are constantly exposed to the positive and negative effects of diet and lifestyle. Therefore, they are an ideal target cell to assess the nutritional or chemical effect on DNA damage, regardless of their age. Other studies have demonstrated the effect of dietary on DNA repair in lymphocytes in as little as 21 (Riso et al., 1999) and 24 days (Guarnieri et al., 2008).

DNA damage has been positively associated with prostate cancer risk (Lockett et al., 2006), hence increased DNA protection and repair is a highly desirable outcome, further supporting the benefit of a diet high in antioxidants and low in saturated fat. Specific foods and nutrients, particularly antioxidants and polyphenol compounds, can positively affect DNA repair (Duthie et al., 1996; Giovannelli et al., 2002; Machowetz et al., 2007; Guarnieri et al., 2008). For example, consumption of green tea (Kanwal et al., 2014), broccoli (Riso et al., 2010) and vitamin C intake (Fraga et al., 1991) have been associated with increased DNA repair in previous studies, while increases in DNA damage have been attributed to oxidative stress (Freitas et al., 2012; Kundu & Surh, 2012) and peroxidation of fatty acids (Gropper, Stepnick & Smith, 2013). The benefit of a Mediterranean diet on markers of DNA damage has been

reported in women with the metabolic syndrome (Mitjavila et al., 2013). As far as the authors are aware, this has not previously been reported in men with prostate cancer

Diet is a complex interaction of a wide range of foods and numerous individual compounds. Genetic and epigenetic modifications can be affected by dietary phytonutrients, which modulate DNA methylation and may induce or enhance DNA repair, the isolation of these compounds is a commonly used, but reductionist approach, to nutritional research. In this study, dietary adherence scores informed a comparison of the adoption of the diet as a whole, as well as the integration of various aspects of it. The aspects of this diet that study participants found the most acceptable were the incorporation of whole grains, olive oil, pomegranate juice, substitution of red meat for chicken, and reducing consumption of sweetened beverages. Each of these achieved >85% compliance overall. On the other hand, the least embraced components were inclusion of *sofrito*, green tea, vegetables, broccoli, and adoption of recommended guidelines for alcohol (in particular red wine). While compliance on these latter items was less than 60%, changes in most did reach statistical significance (Tables 2, 4 and 5).

It is apparent from the inverse association of adherence to the recommended diet with DNA damage that this overall dietary pattern could be of benefit for men with prostate cancer. An inquiry into relationships between individual food items and the benefits seen on this diet aids in justification of continued inclusion or otherwise in future studies. Such data is particularly useful when recommending the incorporation of foods that may be considered unusual and to support the development of strategies to aid increased compliance with less accepted recommendations.

While participants indicated that they were more inclined to choose chicken over red meat, overall complicity to the criteria for restriction of red meat consumption (to less than once weekly) did not indicate that this had actually occurred. In general, New Zealand consumption of beef and lamb is high (FAO, 2013), which is reflected in the baseline data. At the beginning of the study participants were consuming almost 4 serves of red and/or processed meat per week. Hence, while the reduction noted was significant ( $p < 0.001$ ), intake was still higher than requested, suggesting that minimising red meat was a difficult change for participants to make. This may have been caused or compounded by the fact that this study was conducted over the summer period. The New Zealand summer coincides with the festive season, during which barbeques, as social events, are a common aspect of the culture. Thus avoidance of red meat may have been challenging for some participants. If indeed this was a major factor, it also raises the possibility that consumption of pro-carcinogenic heterocyclic amines, as is associated with meat cooked at high temperatures (Norrish et al., 1999), may have negated some of the benefits of the overall diet.

Green tea was not well accepted, with palatability being the reported obstacle. Nevertheless, green tea intake was associated with significant reduction in DNA damage ( $p = 0.002$ ). This is in alignment with the remarkable antioxidant and anti-inflammatory properties associated with green tea, which contribute to its effect on DNA methylation (Julie & Tim, 2012). Green tea consumption was reported by 25% of participants at baseline and 60% at study end. This relatively low uptake, but notable benefit, suggests that the incorporation of a beneficial dietary component may result in substantial gains, even if target levels are not attained.

No associations were noted for broccoli intake, which is in contrast to other reports (Latté, Appel & Lampen, 2011; Ferguson & Schlothauer, 2012). However, the inverse correlation noted between folate



intake and DNA damage is consistent with current understanding of the role of folate in DNA methylation (Gropper, Stepnick & Smith, 2013), and concurs with a recent study in which folate's role in DNA stability was demonstrated (Ong, Moreno & Ross, 2011). In the current study, folate intake was calculated from diet diaries, and broccoli intake was determined from an adherence questionnaire, which was not sensitive to other sources of either folate or other cruciferous vegetables.

The role of vitamin C in regards to cancer is conflicting (Fraga et al., 1991; Herbert et al., 2006) making the finding of this study difficult to compare with other research. A dose-response relationship has been observed in regards to protection from DNA damage, with increasing vitamin C benefiting those with baseline low levels (Herbert et al., 2006; Freitas et al., 2012). In our study a significant inverse association was apparent between vitamin C intake and DNA damage ( $p = 0.007$ ) at study end. Dietary vitamin C in the cohort was not low (Table 4), nor were any of the participants current smokers, which increases vitamin C requirements (Fraga et al., 1991). Examination of the data indicated that the source of this water soluble antioxidant shifted from fruit at baseline to vegetables at the end of the study. However, overall vegetable intake did not change. Furthermore, vegetables are more likely to be consumed cooked, which reduces vitamin C content (Gropper, Stepnick & Smith, 2013). Together, this suggests that vitamin C was not solely associated with the effect noted, but rather, that a nutrient-nutrient interaction, such as with vitamin E, may have occurred. This is congruent with current understanding of the synergistic relationship that exists between these two antioxidant vitamins (Gropper, Stepnick & Smith, 2013). A large prospective study by Wright *et al.* (Wright et al., 2007) suggested that dietary (but not supplemental) vitamin E may be an important nutrient in reducing the risk of advanced prostate cancer. In general, diet is a complex interaction of phytonutrients and it is an accumulative, and/or synergistic effect of these that confers overall benefit. In other words, overall dietary patterns are possibly more important than individual components.

The ethnic homogeneity of the group in the current study meant that the influence of variances in genetic expression was reduced. However, a number of other confounders, including genetic influences, were not controlled for as this would have rendered the group too small for meaningful analysis. The authors recognise the importance of gene-diet interactions and acknowledge that any testing related to genetic expression requires a larger study to demonstrate relevance. Despite the fact that this was a small feasibility study, positive outcomes were noted within a short time frame. In order to apply the findings to a general population, it may first be necessary to confirm the results with a larger cohort.

## Conclusions

We demonstrated that dietary change towards a Mediterranean-style pattern is both achievable and beneficial for men with prostate cancer in New Zealand, albeit in a small and motivated group. This study shows that a holistic approach to diet may contribute to modulation of DNA damage in spite of low baseline levels of inflammation. This is quite possibly due to an undeterminable synergistic effect of dietary components and associated phytonutrients.

Reduction in DNA damage was significantly associated with intake of green tea, legumes, dietary vitamin C and folate, as was overall conformity to the general dietary pattern. While no effect on inflammatory markers was demonstrated, baseline inflammation in this small cohort was low.



Nonetheless, the results obtained add weight to the notion that a low-inflammatory, high antioxidant diet may be of benefit for men with prostate cancer.

Certain aspects of the diet were more acceptable to participants than others. An exploration of the challenges faced in integration of specific dietary components would inform strategies to encourage ongoing compliance, and ultimately, long-term benefit for men with prostate cancer.

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## Author Contributions

KSB planned and initiated the study. SE and KSB carried out the study, planned, and edited the manuscript. SE carried out the Comet assays and wrote the manuscript. SE and NK interpreted the results and edited drafts of the manuscript. DYH carried out the statistical analysis. LRF edited drafts of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest. Companies who donated food items for the study were not involved (financially or otherwise) in the study design, approval, writing or publication of the manuscript.

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