Review

Can the Mediterranean diet prevent prostate cancer?

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Prostate cancer is the second most common cancer in men worldwide. Despite the global importance of this cancer, until recently little was known about risk factors apart from the well-established factors: age, family history and country of birth. The large worldwide variation in prostate cancer risk and increased risk in migrants moving from low to high risk countries provides strong support for modifiable environmental factors. We have based our review on the findings of a systematic review undertaken by an expert panel on behalf of the World Cancer Research Fund and the American Institute for Cancer Research, and new data since then, linking identified foods and nutrients with prostate cancer. Evidence indicates that foods containing lycopene, as well as selenium and foods containing it, probably protect against prostate cancer, and excess consumption of foods or supplements containing calcium are a probable cause of this cancer. The expert panel also concluded that it is unlikely that β-carotene (whether from foods or supplements) has a substantial effect on the risk of this cancer. A recent review on environmental factors in human prostate cancer also found that there were protective effects of vitamin E, pulses, soy foods and high plasma 1,25-dihydroxyvitamin D levels. The Mediterranean diet is abundant in foods that may protect against prostate cancer and is associated with longevity and reduced cardiovascular and cancer mortality. Compared with many Western countries Greece has lower prostate cancer mortality and Greek migrant men in Australia have retained their low risk for prostate cancer. Consumption of a traditional Mediterranean diet, rich in bioactive nutrients, may confer protection to Greek migrant men, and this dietary pattern offers a palatable alternative for prevention of this disease.

Keywords: Lycopene / Mediterranean diet / Olive oil / Prostate cancer / Selenium

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1 Introduction

The purpose of this review paper is to evaluate the evidence linking the Mediterranean diet to low prostate cancer risk and to identify which elements of the Mediterranean diet are likely to protect against prostate cancer.

The recent systematic review undertaken by an expert panel on behalf of the World Cancer Research Fund and the American Institute for Cancer Research (WCRF–AICR) provides an excellent summary of the evidence up to 2005 linking foods and nutrients to prostate cancer [1]. Our review is based on the findings of the systematic review and other more recent publications, and how these relate to the Mediterranean diet.

The focus of the systematic review by the expert panel was on the impact of individual foods and nutrients and their association with prostate cancer [1]. Although the report includes a brief overview of dietary patterns, including the Mediterranean diet, here we will undertake a more in-depth examination of the association between the Mediterranean cuisine and prostate cancer risk.

The Mediterranean diet encompasses a number of eating patterns of people living in countries that border the Mediterranean Sea. The Mediterranean eating patterns include olive oil as the main added fat and an abundance of fresh fruits, vegetables, and nuts that could be important in the prevention of cancer.

The traditional Mediterranean diet of Crete prior to the 1960s, as described in the Seven Countries Study [2], was rich in a number of cancer protective substances such as n-3 fatty acids, a wide range of bioactive phytochemicals

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Abbreviations: ALA, α-linolenic acid; **CVD,** cardiovascular disease; **EPIC,** European Prospective Investigation into Nutrition and Cancer; **DHA,** docosahexaenoic acid; **EPA,** eicosapentaenoic acid; **FFQ,** food frequency questionnaire; **WCRF–AICR,** World Cancer Research Fund and American Institute of Cancer Research Report; **1,25[OH]2D,** 1,25-dihydroxyvitamin D

including lycopene, resveratrol and polyphenols, and vitamins E and C which have all been associated with reduced risk of a number of cancers [3]. However, the impact of the traditional Mediterranean diet as a whole on prostate cancer risk has not been well evaluated.

2 The Mediterranean diet

The Mediterranean diet is characterized by an abundance of a wide variety of plant foods (fruits, vegetables – particularly wild edible leafy greens, wholegrain cereals, nuts, and legumes), olive oil as the principal source of fat and minimal use of other added fats, low intake of red meat, moderate to low intake of dairy foods (mostly as cheese and yogurt), moderate to high intake of fish and moderate intake of wine, normally taken with meals [4, 2, 5]. There are many Mediterranean diets; as many as there are countries with coasts on the Mediterranean Sea [6, 7]. However, the traditional Cretan Mediterranean diet is considered the archetypal Mediterranean diet, and most of the focus on the health benefits of the Mediterranean diet have centered on the Cretan diet. Greater adherence to the traditional Mediterranean diet has been associated with longevity in the elderly [8–10]. The health benefits of the traditional Cretan Mediterranean diet have been attributed in part to the high content of plant-derived bioactive phytochemicals (such as carotenoids, flavonoids, and polyphenols) from fruits, vegetables, olive oil, and wine, which could play a significant role in reducing chronic disease, particularly cardiovascular disease (CVD) [4, 11–15] and a number of cancers [16]. The Lyon Diet Heart Study, well known for the impressive reduction in mortality from cardiovascular events following consumption of a modified Cretan Mediterranean diet, also demonstrated reduced cancer rates in subjects consuming the Cretan diet [17].

Simopoulos and Sidossis [7] in their review of the health benefits of the traditional diet of Greece provide the following summary as to what is so special about the Greek diet [7]:

(i) A more balanced intake of essential fatty acids from vegetable, animal, and marine sources, omega-6:omega-3 ratio of about 2:1 instead of 10:1 or 20:1 as it is in Europe and the U.S., respectively.

(ii) Bioactive phytochemicals: high amounts of vitamin C, vitamin E, β-carotene, glutathione, phytoestrogens, and phytochemicals from green leafy vegetables, phenolic compounds from wine and olive oil; high intakes of tomatoes, onions, garlic, and herbs, especially oregano, mint, rosemary, parsley, and dill that contain lycopene, allylthiosulfinates, salicylates, carotenoids, indoles, monoterpenes, polyphenols, flavonoids, and other phytochemicals.

The high content of bioactive phytochemicals in the Mediterranean diet is of particular interest in the prevention of cancer.

3 Prostate cancer incidence

Prostate cancer is the second most common cancer in men worldwide and it is the sixth most common cause of death in men [1]. The incidence of prostate cancer has dramatically increased over the past few decades, thought to be primarily due to the early detection measures, such as prostate specific antigen testing and transrectal ultrasound guided prostate biopsy, and increased public awareness [18, 19].

Prostate cancer incidence varies significantly around the world, with the highest age-standardized rates reported in the United States (125 cases *per* 100 000 males *per* year), New Zealand (101 cases *per* 100 000 males *per* year), and the Nordic countries: Sweden (91 *per* 100 000 males *per* year), Finland (84 *per* 100 000 males *per* year), and Norway (82 *per* 100 000 males *per* year). Australia's incidence is similar to the Nordic countries at 76 cases *per* 100 000 males *per* year, and significantly higher than southern European countries such as Italy (40.5 *per* 100 000 males *per* year) or Greece (26 *per* 100 000 males *per* year) [20]. Incidence rates in China, Japan, and South-Eastern Asia are particularly low (1.7, 12.6, and 7.0 cases *per* 100 000 males *per* year, respectively), although it is argued that incidence data are confounded by the extent to which PSA and digital rectal screening are used [20]. The incidence of prostate cancer in Australia increased dramatically in the early 1990s, as in most Westernized countries, due to improved detection methods, however mortality rates have remained relatively stable for over five decades in men aged less than 85 years [20]. Prostate cancer mortality rates in Australia (18 *per* 100 000 males *per* year) are lower than Norway or Sweden (28 *per* 100 000 males *per* year) but higher than Greece (11 *per* 100 000 males *per* year), Italy (12 *per* 100 000 males *per* year), Japan (5.7 *per* 100 000 males *per* year), South-Eastern Asia (4.5 *per* 100 000 males *per* year), and China (1.0 *per* 100 000 males *per* year).

There is significant within country variation in prostate cancer incidence associated with ethnicity and geographic region. The most striking within country variations in incidence are seen in the USA, where incidence varies from very low levels in the Chinese in Los Angeles (33.4 cases *per* 100 000 men) to very high levels in the black population of Michigan, Detroit (202 cases *per* 100 000; GLOBOCAN, 2002; http://www-dep.iarc.fr/; accessed 1st May 2008).

Interestingly, Greek migrants to Australia appear to have retained their low prostate cancer risk despite being in Australia for 50 years, the majority arriving in the 1950s and 1960s after the Second World War [21]. Recent data from the Victorian Cancer Registry shows that men born in Greece have the lowest age-standardized prostate cancer incidence (56.4 cases *per* 100 000 persons *per* year) compared with men born in the UK (82.6 cases *per* 100 000) or Australia (111.4 cases *per* 100 000) (Thursfield, V., Victorian Cancer Registry, The Cancer Council Victoria, Melbourne; personal communication).

Greek migrants in Australia have been the focus of considerable research interest because they have retained a lower all-cause mortality profile (primarily due to CVDs and major cancers) than the Australian-born population, despite 50 years postmigration [22]. Greek migrants appear to have retained the important components of their traditional Greek Mediterranean dietary pattern, in contrast to other migrant groups who rapidly acculturate to their new country [23–25]. Dietary studies of Greek migrants in Australia have shown that although some changes to food intake patterns occurred soon after migration (namely more meat and dairy foods), they have retained their high intakes of fresh fruits, vegetables, cereal, nuts, pulses, and olive oil, which could protect them from premature cardiovascular and cancer mortality [8, 23, 26, 27].

4 Nutritional etiology and prostate cancer

The prostate gland is a walnut-sized gland, forming part of the male reproductive system, which produces seminal fluids to nourish sperm cells in the ejaculate. The growth and function of the prostate are controlled by testosterone and the three most common prostate disorders are enlargement (benign prostatic hyperplasia), inflammation (prostatitis) and cancer.

Prostate cancer develops over many decades and it has been postulated that all men would have prostate cancer if they lived beyond 100 years [28].

Prostatic growth and development depend on androgens, and studies of prostate cancer and sex hormone levels have been based on the hypothesis that high levels of androgens, particularly testosterone, the main circulating androgen, increase prostate cancer risk [29, 30]. Epidemiological evidence has not supported this association. A meta-analysis of 10 prospective studies in 1999 found no association between serum testosterone or dihydrotestosterone (DHT) and prostate cancer; and a possibly higher concentration of androstanediol glucuronide in cases compared with controls in one study [31]. Studies performed since have also not supported the androgen hypothesis [32]. Severi *et al.* [32] reported from the MCCS that high baseline levels of serum testosterone were associated with more aggressive prostate cancer, but not localized prostate cancer, and this association with more severe forms of prostate cancer has been noted elsewhere [30]. The Prostate Cancer Prevention Trial demonstrated that finasteride (a 5α-reductase inhibitor, *i.e.*, blocks the synthesis of DHT from testosterone) reduced the period prevalence of prostate cancer by 24%, but the treated men had a higher period prevalence of higher grade cases [29]. This lack of a simple association between androgens and prostate cancer is consistent with the inconclusive studies on the benefits of soy phytoestrogens; postulated to reduce the risk of prostate cancer *via* estrogenic or antiandrogenic effects [33]. Clearly the role of androgens in prostate cancer development needs to be studied further.

There is now strong evidence that environmental factors play an important role in the etiology of prostate cancer. Prostate cancer incidence rates vary across countries as noted above, and men who migrate from low risk to high risk countries typically develop the higher risk of their destination country [19, 34, 35]. However, as noted previously Greek migrant men in Australia have retained their low prostate cancer risk despite more than 50 years since migration [22].

The association between diet and cancer dates back to the 1981 landmark report by Doll and Peto [36] who estimated that 35% of cancers in the USA were attributable to diet. In a 2005 commentary on diet and cancer Willett argues that the evidence from prospective studies for an association between prostate cancer (and other cancers) and diet is weak due to limitations in measuring dietary intake and the lack of data on diet during childhood, which may be a critical period where diet can modify cancer risk [37]. Most cancers develop to the stage of being clinically identifiable only years or decades after the initial DNA damage, therefore environmental factors such as diet that may impact in the early stages of cancer development may not be captured by current studies [1]. Nutrition may also play a role in modifying the later stages of the cancer development process [1], and the importance of dietary changes in later life is evidenced by changes in cancer risk in people who move to higher risk countries as adults.

The WCRF–AICR expert panel concluded that foods containing lycopene and selenium probably protect against prostate cancer, and diets high in calcium are a probable cause of this cancer. The evidence for other nutrients or food groups is limited [1]. While the findings of a recent review of environmental factors in human prostate cancer (published since the WCRF–AICR report) were consistent with this, they also concluded there was strong epidemiological evidence for a protective role of vitamin E, pulses, soy foods, and high plasma 1,25-dihydroxyvitamin D (1,25[OH]2D) levels [38].

There are a number of plausible mechanisms by which nutrients in foods may protect against prostate cancer. Following the publication of the WCRF–AICR expert panel report, a detailed review of the associations between foods and prostate cancer was published (January 2008 issue of this journal) providing a detailed description of the mechanisms of action of different foods on prostate cancer development [39]. The findings of this review will be discussed in the relevant sections.

5 Dietary fats and prostate cancer

The association between total dietary fat and prostate cancer was first noted by Doll and Peto [36]. Early epidemiological studies compared national food consumption data and prostate cancer incidence, identifying associations

between individual foods (particularly fats) and prostate cancer risk [40, 41]. Of particular interest was the low prostate cancer incidence in Asian populations, and it was postulated that their very low fat diet (among other dietary factors such as green tea and soy products) was protective for prostate cancer [35].

Although the 1997 WCRF–AICR expert panel concluded that saturated fat of animal origin and total fat was positively associated with prostate cancer risk [42] the recent WCRF–AICR expert panel concluded that there was inconsistent and limited evidence supporting an association between total dietary fat and prostate cancer [1]. A recent analysis of dietary fat intake and prostate cancer risk in the European Prospective Investigation into Nutrition and Cancer (EPIC) also concluded that there is no association between dietary fat and prostate cancer risk [43].

There are however, some interesting associations between specific types of fats and prostate cancer risk, with relevance to the Mediterranean diet, that are worth noting.

5.1 Monounsaturated fatty acids

The Seven Countries Study was the landmark study that generated interest in the Mediterranean diet [2]. The results of the 5 year follow-up showed that the population from Crete in Greece had the lowest rates of CVD and cancer mortality and the investigators attributed this to their diet: specifically the low saturated fat and high monounsaturated fat intake, nearly all from olive oil [2]. Olive oil is an integral ingredient in all Mediterranean diets, and olive oil (most likely extra virgin and unprocessed) comprised 95% of all added fats in the traditional Cretan Mediterranean diet of the 1960s [2]. Olive oil is typically consumed with vegetables and legumes, increasing the palatability of these foods and facilitating higher intakes [44]. Therefore it is difficult (in epidemiological studies) to tease out the effects of olive oil from the abundant protective ingredients in the Mediterranean diet. The beneficial effects of olive oil in cancer prevention are thought to be due to the high concentration of antioxidants in olive oil (particularly extra virgin) [45], the resistance of oleic acid to oxidative modification [46], and the high concentration of polyphenols with anti-inflammatory potential [47].

Recent evidence from *in vivo* studies has shown that oleic acid, the predominant MUFA in olive oil, has the ability to regulate cancer-related oncogenes [48] however; there are no known studies at present investigating the impact of oleic acid on human prostate cancer growth.

5.2 N-3 polyunsaturated fatty acids

5.2.1 α-Linolenic acid (ALA)

In a meta-analysis of nine cohort and case–control studies examining dietary α-linolenic acid (ALA; 18:3 n-3) and prostate cancer mortality the authors concluded that high intakes of ALA could increase the risk of prostate cancer by about 70% [49]. The authors cautioned that the results were heterogeneous, with one study indicating a slightly protective effect of ALA intake. Dietary ALA can come from different sources including meat and vegetable oil, and hence the positive association between ALA and prostate cancer may be confounded by the form in which it is consumed and other nutrients that occur with it [49]. Supplementation of ALA from ground flaxseed appeared to decrease tumor growth in men with prostate cancer [50]. In high risk populations ALA may be a marker for meat consumption. The mechanisms by which ALA can cause prostate cancer are poorly understood, but it is postulated that ALA is associated with prostate cancer *via* free radical damage and elevation of IGF-1 levels [39].

Other studies have suggested that n-3 PUFAs are protective against cancer mortality. The Lyon Diet Heart Study, a randomized intervention trial of a Cretan diet rich in ALA from margarine and canola oil that was provided, demonstrated that the patients who developed cancer had significantly lower plasma n-3 fatty acids [18].

Simopoulos argues that the benefits of the traditional diet of Crete should be attributed to the significantly higher concentrations of n-3 fatty acids (ALA, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the latter are predominantly from marine sources), as well as to olive oil, wine, fruits, and vegetables [51]. For example, wild edible greens, and snails collected from the field are both rich sources of ALA and are traditional to the Cretan Mediterranean diet. Purslane, a commonly eaten wild edible green, contains much more ALA at 4.05 mg/g than spinach (0.89 mg/g) or butter lettuce (0.26 mg/g) [3]. Free range hen eggs from a Greek village had an n-6:n-3 ratio of 1.3 (6.9 mg ALA/g egg yolk) compared with an n-6:n-3 ratio of 19.4 (0.52 mg ALA/g egg yolk) for an American supermarket egg [7]. This can be explained by the significant differences in the diets of the hens: with the village hens being truly "free range" and eating wild greens, worms and insects (rich in n-3), while the American hens were fed on n-6 rich stock feed in common with other intensively reared animals in the US.

5.2.2 EPA and DHA

In the Seven Countries Study, the Japanese cohort had the second most favorable mortality rates from CVD and cancer after the Cretan cohort; however unlike the Cretan cohort who consumed a high fat diet (37% energy from fat), the diet of the Japanese was the lowest in total fat (11% of energy from fat) [2]. Interestingly, both the Japanese and Cretan cohorts consumed significantly more fish that the other cohorts, hence their diets were relatively high in long chain n-3 fatty acids [2, 3]. The reduced prostate cancer risk in many Asian populations, particularly the Japanese, has been attributed to their high intake of fatty fish rich in long chain omega-3 fatty acids [52].

The cardioprotective effects of long chain n-3 fatty acids (EPA and DHA) have been confirmed by epidemiological and clinical intervention studies [53, 54]; however the protective effects of these fatty acids on prostate cancer are poorly understood. The long chain n-3 fatty acids EPA and DHA are thought to be protective for prostate cancer due to their anti-inflammatory effects and their ability to modulate the expression of a number of molecular parameters involved in prostate carcinogenesis in vitro (COX-2 enzymes, nuclear factor-κB, and PPARγ) [55].

It appears, therefore, that ALA may be positively associated with prostate cancer risk whereas the long chain n-3 fatty acids EPA and DHA may be protective for prostate cancer risk. As the majority of studies on fatty acids and prostate cancer are population studies or *in vitro* cell line studies, human clinical intervention studies are required to clarify the potential protective or adverse effects of n-3 fatty acids on prostate cancer risk.

5.2.3 N-6 fatty acids

There is some concern that changes in the ratio of n-6 to n-3 fatty acids from around 1:1 in the Paleolithic diet to over 10:1 with the widespread use of seed oils and margarines in Western diets may have adverse health effects [3, 56]. However, a 2004 review found no evidence that n-6 fatty acids were associated with prostate cancer [57], and the WCRF–AICR expert panel did not report on any association between n-3 or n-6 fatty acids and prostate cancer [1].

The traditional Mediterranean diet is high in oleic acid (primarily from olive oil), moderately low in linoleic acid, moderately high in ALA (primarily from plant sources), and high in long chain n-3 fatty acids EPA and DHA [37, 44, 51]. This traditional diet may therefore have the optimal fatty acid profile for the prevention of prostate cancer.

6 Vegetables and prostate cancer

The WCRF–AICR expert panel concluded that there is limited evidence suggesting that legumes protect against prostate cancer [1], although the recent review by Wigle *et al.* [38] suggests that soy foods may reduce prostate cancer risk. It is postulated that phytoestrogens, such as isoflavanoids, from soy products and other legumes may play an important role in inhibiting testosterone-induced tumor growth. The low incidence of prostate cancer in Asian populations may be partly due to their high intake of phytoestrogens from soy products, and polyphenols from green tea [35]. A Japanese case–control study investigating prostate cancer risk and diet showed that men who consumed beancurd and other fermented legume products had reduced risk of prostate cancer [52]. The isoflavonoid genistein has been shown (in *in vitro* studies) to suppress DNA synthesis and induces apoptosis in human prostate cell lines [58]. A Chinese case–control study investigating consumption of green tea and prostate cancer risk demonstrated that consumption of more than 3 cups green tea *per* day reduced prostate cancer risk by 73% [59]. The polyphenol in green tea, epigallocarechin-3-gallate, has potent antioxidant activity and induces apoptosis in human prostate cancer cell lines *in vitro* [60].

Phytosterols are the plant equivalent of cholesterol, and share a similar structure to cholesterol. Dietary phytosterols, added to spreadable fats and more recently dairy foods, are commonly used to reduce cholesterol absorption, by displacing cholesterol from intestinal micelles. The main dietary sources of phytosterols are unrefined plant oils, seeds, nuts, and legumes, all abundant in the Mediterranean diet. One of the most common dietary phytosterols β-sitosterol has been shown to reduce tumor growth in a human prostate cancer cell line [61].

Of relevance to the Mediterranean diet is the study by Hodge *et al.* [62], a case–control study including 858 men in Australia with prostate cancer found that tomatoes, tomato-based foods and allium vegetables were protective for prostate cancer and proposed that a Mediterranean-type diet which is abundant in tomatoes, onions, and garlic could be protective for prostate cancer. Cruciferous vegetables, such as broccoli, cauliflower, and cabbage, abundant in a traditional Mediterranean diet, have demonstrated anticarcinogenic properties in animal models and *in vitro* studies [63, 64]. Consumption of three or more servings of cruciferous vegetables *per* week, compared with less than one serve *per* week was associated with 41% reduction in risk of newly diagnosed prostate cancer [65]. More recently, Kirsh *et al.* [66] reported that a high intake of cruciferous vegetables may be associated with a reduced risk of aggressive prostate cancer. Despite these findings the WCRF–AICR expert panel concluded that there was no association between consumption of cruciferous vegetables and prostate cancer [1]. Although the consumption of fruits and vegetables was inversely associated with the incidence of all cancers in the Greek cohort of EPIC [67], there was no association between the consumption of fruits and vegetables and the risk of prostate cancer in an analysis of 130 544 men in 7 countries in EPIC [68, 69].

There are clearly protective effects of selected vegetables, such as tomatoes (discussed later), on prostate cancer risk, however the association of prostate cancer risk with total vegetable intake may be confounded by bulky starchy vegetables with low antioxidant content such as potatoes, and by measurement error as people tend to over-report intake of fruits and vegetables, particularly using a food frequency questionnaire (FFQ) [70, 71].

7 Selected nutrients and prostate cancer

7.1 Lycopene

Lycopene is one of the most potent carotenoid antioxidants and has been shown to exert antiproliferative effects on

prostate cancer cells by inhibiting IGF-1 stimulated prostate cancer cell growth *in vivo* and in animal models [72].

By far the most consistent evidence for a protective effect of diet on prostate cancer risk is for tomatoes and tomato products and the plasma biomarker lycopene [1, 73]. In a meta-analysis of cohort data on serum or plasma lycopene the WCRF–AICR expert panel concluded that for every 10 mg/L increase there was a 4% reduction in prostate cancer risk [1]. In a recent analysis of plasma carotenoid concentration and prostate cancer risk in 137 001 men from EPIC, there was no association between plasma lycopene and localized prostate cancer however men in the highest quintile of plasma lycopene levels had a 60% reduced risk for advanced prostate cancer [74]. The Health Professionals Follow-up Study showed that 2–4 serves of tomato sauce (an important source of lycopene in the USA) *per* week was associated with a 35% reduction in prostate cancer risk [73]. Tomatoes and tomato products such as fresh pasta sauces and sauces in vegetable casseroles are key ingredients in a traditional Mediterranean diet, however tomatoes are nearly always consumed with olive oil and, in the case of cooked meals also with allium vegetables, thus providing a rich array of bioactive phytonutrients [10, 51]. Consuming cooked tomatoes with olive oil increases the bioavailability of lycopene [75] as well as the palatability of the meal [44].

7.2 β-Carotene

The WCRF–AICR expert panel concluded that there was strong evidence from cohort studies and clinical trials that β-carotene does not have a protective effect on prostate cancer risk [1]. A recent Cochrane review on antioxidant supplements and mortality concluded that β-carotene, vitamin A, and vitamin E supplements (given as single supplements or in combination with other antioxidant supplements) significantly increase mortality from all causes [76].

The Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study investigated the impact of supplementation with α-tocopherol and β-carotene, given singly or in combination, on the risk of lung cancer in smokers [77]. After 6 years there was a 15% increase in lung cancer and an 8% increase in all-cause mortality in subjects on β-carotene. The group supplemented with α-tocopherol had a 34% reduction in prostate cancer incidence but no effect on lung cancer or all-cause mortality [78]. Antioxidants may have dual roles, and although normal quantities obtained from the diet may have a number of beneficial anticancer effects, particularly in individuals with poor intakes [79], excessive quantities given *via* supplementation can have severely adverse effects acting as pro-oxidants and promoting cancer [76].

Plasma β-carotene is an important biomarker of dietary intake of vegetables, particularly carrots in an Australian population [80] and also a good marker of adherence to the Mediterranean diet [81], however the primary sources of β-carotene in the Mediterranean diet are green leafy vegetables which are also rich in lutein/zeaxanthin, and other plant-derived antioxidants [82].

7.3 Selenium

The WCRF–AICR expert panel report concluded that foods containing selenium probably protect against prostate cancer [1]. There is also strong evidence from clinical trials that selenium supplementation probably protects against prostate cancer [1]. A meta-analysis of 16 studies (11 cohort and 5 case–control) found that any intake of selenium (average intake between the first and fourth quintile relative to the lowest intake category) was associated with a 28% reduced risk of prostate cancer for cohort studies and 26% reduced risk for case–control studies [83]. The Nutritional Prevention of Cancer Trial, a randomized trial of selenium (200 μg/day) in USA residents, demonstrated a 50% reduction in overall incidence of prostate cancer in the supplemented group [84]. However, this trial also showed an increase in the risk of squamous cell carcinoma and total nonmelanoma skin cancer with 200 μg/day selenium supplementation in individuals at high risk of nonmelanoma skin cancer [84]. Although the impact on skin cancer risk in a low risk population is not known, this finding highlights the importance of adequate but not excessive consumption for disease prevention. The selenium and vitamin E cancer prevention trial (SELECT), one of the largest studies of chemoprevention for prostate cancer, recruited 32 400 men in 2001 and early data suggest both selenium and vitamin E supplementation may prevent prostate cancer [85]. Selenium's cancer protective effects are thought to be due to induction of apoptosis, prevention of cellular proliferation and inhibition of cellular damage secondary to free radical production *via* its role as a cofactor for glutathione peroxidase which protects against oxidative tissue damage [83, 86].

Dietary sources of selenium include fish, meat, eggs, and cereals, and composition varies by geographic region depending on the selenium content of the soil that foods are grown in or animals are grazed on [87]. Simopoulos reports that the traditional Cretan Mediterranean diet of the 1960s was high in selenium from fish and seafood, particularly octopus, which is a favorite Greek appetizer [3].

7.4 Vitamin D

Low levels of plasma 1,25[OH]2D or 25[OH]D are associated with increased prostate cancer risk in some populations but not others [38]. The Physician's Health Study identified a significant level of vitamin D insufficiency in men; almost one-third were deficient in plasma 25[OH]D levels (<20 ng/mL) and more than two-thirds had insufficient plasma 25[OH]D levels (<32 ng/mL). Men with plasma levels of (25[OH]D) below compared with above the

median had a two-fold risk of developing aggressive prostate cancer [88]. The prohormone vitamin D is obtained *via* UV exposure and from the diet, and is converted to (25[OH]D) in the liver [89]. Circulating 25[OH]D is a sensitive marker of vitamin D status and in many tissues, including the prostate, 25[OH]D is further converted to the active form 1,25[OH]2D, which operating through vitamin D receptors, inhibits cell proliferation, promotes angiogenesis, and induces differentiation and apoptosis [89, 88]. The active form 1,25[OH]2D slows prostate tumor growth and prevents prostate cancer metastases in rodent models [90] and this mechanism may help explain why low vitamin D status significantly increases prostate cancer risk in men.

The Mediterranean diet is adequate but not particularly high in vitamin D. However, people of the Mediterranean region may be protected from an increased risk of many solid cancers, including prostate cancer, due to their prolonged exposure to the sun resulting in improved vitamin D status. A recent study of more than 4 million people in 11 countries found that prolonged exposure to the sun, as determined by nonmelanoma skin cancer, reduced the risk of several solid cancers, especially stomach, liver and gallbladder, pancreas, lung, breast, bladder, kidney, and prostate cancer, particularly in sunny countries such as Spain [91]. Although Greece was not specifically mentioned in this study it has a very similar climate to Spain and sun exposure would be similar. Greek migrants in Australia appear to have retained traditional lifestyle factors such as maintaining vegetable gardens [8], which provides them with considerable sun exposure in a country considered to be sunny [91].

7.5 Calcium

High dietary calcium, although beneficial in the prevention of osteoporosis, may be associated with increased risk of prostate cancer [1, 38]. The WCRF–AICR expert panel concluded that diets high in calcium are a probable cause of prostate cancer [1]. A recent meta-analysis of dairy product and calcium intake demonstrated a small but significant increase in prostate cancer risk in men with the highest relative to lowest intake (categories) of dairy foods (11% increase) and calcium intake (39% increase) [92]. The Health Professionals Follow-up study found an increased risk of advanced or fatal prostate cancer with calcium intakes (from diet and supplements) in excess of 1500 mg/day [93]. It is postulated that a high calcium intake, from dairy foods and other sources, increases the risk of prostate cancer by suppressing the production of the active form of vitamin D (1,25[OH]2D), which inhibits proliferation of malignant prostate cancer cells as noted above.

The association between calcium intake and prostate cancer is unexpected. It is well known that an adequate calcium intake, primarily *via* low fat dairy foods, is important in the prevention of osteoporosis [94], and many populations have inadequate calcium intakes, prompting governments to develop specific dietary guidelines for increasing dairy food consumption [95, 96]. Diets rich in dairy foods have recently been associated with improved weight loss in type 2 diabetes [97], and protection from the individual components of the metabolic syndrome, obesity, hypertension, dyslipidemia, and hyperinsulinemia [98]. It is possible that the association between dairy foods and prostate cancer is confounded by other dietary components, such as saturated fat, or high energy intakes, or inaccuracies in the dietary assessment of dairy food intake [92].

The traditional Cretan Mediterranean diet of the 1960s was not particularly high in Calcium. Food intake data from the Seven Countries Study showed that the Cretan cohort consumed small modest quantities of cheese (13 g/day) and milk (235 g/day). Together with the small quantities of calcium derived from legumes and leafy vegetables, the daily calcium intake of the Cretans would not have exceeded 400–500 mg/day [2]. However, a recent national survey (using an FFQ) of calcium intakes in Greece reported a mean population intake of 861 mg/day [99]. This is not dissimilar to the calcium intakes of the Australian population estimated at 845 mg/day [100]. It may be the source of calcium or types of dairy foods consumed that are important in the potential adverse effects of calcium on prostate cancer risk. The major types of dairy foods in the traditional Mediterranean diet are derived from goat's milk and sheep's milk which are compositionally different (particularly with respect to the calcium to phosphate ratio) to the widely consumed cow's milk in countries such as Australia and the USA where prostate cancer rates are significantly higher. Furthermore, the traditional Mediterranean diet is rich in oxalic acid and phytic acid from the high quantities of leafy vegetables and wholegrain cereals, which reduces the absorption of calcium from the diet [101]. This warrants further investigation.

In Table 1, we summarize the associations between individual foods and nutrients, relevant to the Mediterranean diet, and prostate cancer risk. Although the effects of individual food components on prostate cancer risk are described, the benefits of the Mediterranean diet may be due to the synergistic effects of combinations of several potentially protective foods and nutrients.

8 Role of the Mediterranean diet in prostate cancer prevention

Most of the available evidence on diet and prostate cancer is centered on individual foods or food groups and isolated nutrients. The WCRF–AICR expert panel report devotes almost 200 pages of review on individual foods or nutrients and cancer and only 6 pages of review on dietary patterns and cancer [1]. Populations consume dietary patterns not individual foods or nutrients. It is now well recognized that

Table 1. Associations of foods and nutrients common to the Mediterranean diet and prostate cancer

Food/nutrient	Association with prostate cancer risk	Dietary sources	Association with Mediterranean diet
Lycopene	(↓) Probably reduces risk	Lycopene is predominantly found in tomatoes and tomato products [68]. Lycopene bioavailability is increased by consuming tomatoes with oil [75]	Tomatoes and tomato products such as fresh pasta sauces and sauces in vegetable casseroles are key ingredients in a traditional Mediterranean diet. Tomatoes are nearly always consumed with olive oil
Selenium and selenium containing foods	(↓) Probably reduces risk	The levels of selenium in plant and animal foods reflect soil levels. In Australia [87] and Greece [7], the highest levels are in fish and marine foods, followed by eggs and cereals	Marine foods are integral to the Mediterranean diet, and octopus, a common appetizer is particularly high in selenium containing 90 μg/100 g [4]
Diets high in calcium	(↑) Probably increases risk. Milk and dairy products are less consistently linked with prostate cancer	The major sources of calcium in the diet are dairy foods. Oxalic acid (in spinach and rhubarb) and phytic acid (in bran), reduce calcium absorption [96]	The traditional Mediterranean diet is moderately low in calcium and the main sources are goat's and sheep's milk which are compositionally different to cow's milk (the main source in most Western diets). Mediterranean diets are high in oxalic acid from leafy greens, which may reduce calcium absorption
Foods containing vitamin E	(↓) Possibly decreases risk	Vitamin E is found in vegetable oils, nuts, and seeds [96]	The main sources of vitamin E in the Mediterranean diets are sunflower and olive oils, nuts, and seeds [4, 105]
Legumes (including soy and soy products) Phytoestrogens Nuts/seeds Phytosterols	(↓) Possibly decreases risk	Legumes consumed in cooked or dry roasted form. Soy consumed as milk, or processed form as protein source. Nuts and seeds consumed whole as snacks or added to breads/cooked dishes/desserts	Legumes (but not soy) are common in Mediterranean diets consumed in bean salads, soups, casseroles, and dried as snacks (*e.g.*, dry roasted chickpeas). Nuts (particularly walnuts and almonds) and seeds (particularly pumpkin and sesame) are commonly consumed as snacks or added to foods
Processed meats	(↑) Possibly increase risk	Sources include sausages and cured meats (salami, ham, mortadella, strassburg)	Processed meats are not commonly consumed in the traditional Greek Mediterranean cuisine
Total and saturated fat	(–) Previously considered to be associated with increased risk of prostate cancer [36], but more recently expert panel concluded no association exists [1]	Sources include diary foods (particularly butter), fatty meats, chicken skin, pastries, processed/cured meats	Med diet is relatively low in saturated fat, but not in total fat
Olive oil	While no studies of olive oil and prostate cancer specifically, potential benefits through antioxidants and oleic acid	Any type of olive oil including, pure, virgin, and extra virgin	Olive oil is the main added fat in the Mediterranean diet and is an integral ingredient in the Mediterranean cuisine. Extra virgin olive oil (rich in antioxidant phytochemicals) is preferred on salads and eaten raw
Omega-3 fatty acids	(↓) Long chain omega-3 fatty acids DHA and EPA may reduce risk. ALA has been associated with risk in some studies	Long chain omega-3 fatty acids are from marine sources. Association of ALA with prostate cancer may depend on dietary sources, as in many diets, e. g., Australia/USA, meat is main source	Mediterranean diets typically include reasonable amounts of fish and sea foods. In Mediterranean diets, ALA is mostly from nonmeat sources, *i.e.*, leafy greens, snails, and from eggs and poultry that have grazed on high n-3 diets (worms, purslane, snails)

dietary patterns rather than individual foods or nutrients are more predictive of disease risk because the overall diet is considered and there is less risk of excluding important components of the diet particularly in diseases with multiple dietary associations such as cancer [102].

A recent review of associations between dietary patterns and prostate health concluded that foods of animal origin that are typical in a Western diet, such as dairy foods and meat and excess energy, were associated with prostate cancer, and foods of plant origin, such as fresh fruits and vegetables, wholegrain cereals, fish, tea, and nuts were protective for prostate cancer [39]. Although little reference was made to dietary patterns or cultural eating habits, reference is made to the importance of whole diet effects and the authors conclude that healthy dietary patterns should ideally be followed through the whole life cycle to be most effective in preventing prostate cancer [39]. The foods and nutrients identified by Stacewicz-Sapuntzakis *et al.* in their review are abundant in the Mediterranean diet.

A recent Australian case–control study examined the association between three dietary patterns (identified using factor analysis) labeled vegetable, Western, and health-conscious, and found that the Western dietary pattern which included meat, milk, and refined grains was positively associated with prostate cancer risk [103]. This study is unique among case–control studies, in that dietary intake was estimated for 10 years prior to disease diagnosis, by an FFQ completed during the study. It may be that dietary data 10 years previously is more relevant in relation to prostate cancer, due to the long latency phase of this disease; this design may also reduce recall bias and effects of recent dietary changes due to the diagnosis of prostate cancer [103].

An examination of the available published literature on the association between consumption of the Mediterranean diet and prostate cancer risk revealed a number of reviews focusing on the Mediterranean dietary patterns and cancers [3, 104–106], however there are few studies specifically focusing on prostate cancer [107].

The association of the Mediterranean dietary pattern and all-cause mortality was investigated in EPIC, a multicenter prospective cohort study established in 1992 to investigate the role of biological, dietary, lifestyle and environmental factors in cancer and other chronic diseases, involving more than 500 000 participants in 23 centers from 10 European countries [16]. Greater adherence to the Mediterranean diet was consistently associated with increased survival among older people across the 10 countries [10]. The association of a Mediterranean eating pattern and mortality was investigated in the National Institutes of Health–American Association of Retired Persons (NIH–AARP) Diet and Health Study, a prospective cohort study of more than 370 000 elderly people in the USA [108]. Greater conformity to a Mediterranean dietary pattern was associated with reduced all-cause mortality (21% reduced risk in men and 20% in women), and mortality from CVD (22% reduced risk in men and 19% reduced risk in women) and cancer (17% reduced risk in men and 12% in women), data for prostate cancer deaths was not shown [108].

One of the few studies on diet and prostate cancer in Greece in the late 1990s examined the association between dietary intake and prostate cancer in 320 cases and 246 controls recruited from 6 hospitals in Athens [107]. The authors concluded that the intake of dietary vitamin E and cooked tomatoes reduced prostate cancer risk and the intake of dairy products and polyunsaturated fats increased prostate cancer risk whereas, no effect was observed for olive oil and no reference was made to a Mediterranean dietary pattern [107].

In an analysis of the potential for prostate cancer risk reduction by switching from a Western diet to a Mediterranean dietary pattern it was concluded that men could reduce their incidence of prostate cancer by 10% by making such a change [104].

With the exception of soy foods all the other foods and nutrients that have been associated with reduced prostate cancer risk are abundant in a Mediterranean-style diet. Interestingly, as noted above the traditional Cretan variant of the Mediterranean diet of the 1960s did not contain large quantities of dairy foods, the only food group that may be positively associated with increased prostate cancer risk. In addition to a healthy dietary pattern, the traditional Mediterranean lifestyle involved extended periods in the in the Mediterranean sun which would impact positively on plasma 1,25[OH]2D levels offering further protection from prostate cancer.

Another important lifestyle factor impacting positively on the diet quality of Greek populations is Greek Orthodox fasting. There are three main fasting periods in the Greek Orthodox religion throughout the year: Christmas (40 days), Lent (48 days), and the Assumption (15 days) [109]. Greek orthodox fasting is characterized by a strict vegan diet resulting in a significant reduction in saturated fat, cholesterol, and calcium intakes from the avoidance of animal products, and increased intakes of fiber and folate from the high consumption of fruit, vegetables, and legumes [109]. Although there are no studies specifically investigating the impact of traditional Greek Orthodox fasting on prostate cancer risk the consequential dietary changes may be positive for prevention of prostate cancer.

9 Conclusions

It is clear that environment plays an important role in the etiology of prostate cancer as men who migrate from low risk countries to high risk countries typically develop the higher risk of their host country, primarily due to the adoption of the diet and lifestyle of their host country. Greek migrant men in Australia on the other hand, have retained their low prostate cancer risk despite 50 years since migra-

tion. These migrants appear to have resisted acculturation and retained many important features of a traditional Mediterranean-style eating pattern, which may protect them from prostate cancer.

There is strong evidence from epidemiological studies supporting positive associations between foods that are typical of a Mediterranean eating pattern and reduced prostate cancer risk; therefore it could be argued that a combination of these foods, as would be achieved in a Mediterranean eating pattern, would have a synergistic effect providing greater protection against prostate cancer. However, most of the research efforts have concentrated on individual foods and nutrients in the hope of finding magic bullets.

Clinical trials on prostate cancer prevention are still focusing on these 'magic bullets' despite the disappointing outcomes of high dose supplementation trials such as the ATBC trial demonstrating an increased all-cause mortality and increased risk of lung cancer in the supplemented group. Prostate cancer supplementation trials have largely had no effect; however preliminary results from the SELECT trial have shown some promise for selenium and vitamin E supplementation and prostate cancer risk reduction.

The findings of the WCRF–AICR systematic review support the intake of tomatoes, tomato products and lycopene as well as selenium and foods containing selenium as being protective for prostate cancer. Little mention is made of dietary patterns and prostate cancer prevention however, it must be noted that populations consume whole diets not individual foods or nutrients. The supplementation trials have taught us some important lessons on the physiological impact of interfering with the balance of nutrients in the diet, particularly β-carotene.

The traditional Mediterranean diet of the 1960s, with the high content of plant-derived bioactive phytochemicals (such as carotenoids, flavonoids and polyphenols) from fruits, vegetables, olive oil, and wine offers a palatable chemo-protective alternative for the prevention of prostate cancer.

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